Towards the plumbemycins: the development of a novel chiron

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TOWARDS THE PLUMBEMYCINS-

THE DEVELOPMENT OF A NOVEL CHIRON .

Submitted by

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for the degree of Doctor of Philosophy

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"Nothing you can do that can't be done"

"All You Need is Love"
the beatles

For my family

ACKNOWLEDGEMENTS.

I owe thanks to a great many people who kept me going during this long march. I would particularly thank my supervisors Professor Malcolm Campbell and Dr. Arthur Floyd for their contributions and Dr. Terry Lewis (of ICI Plant Protection) for added inspiration. I must also thank both the University of Bath and ICI Plant Protection for financial support.

Also important has been the technical assistance (and patience) of Sue,Chris,Dave and Harry and ,latterly, the invaluable typing of my 'pool'- Diana, Paula,Isobel and Mrs Edwards.

Above all I am indebted to all my colleagues, past and present, old and young, for making the miles easier and my friends and family for keeping me 'dancing'.

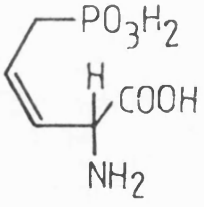
CONTENTS

.ABSTRACT.

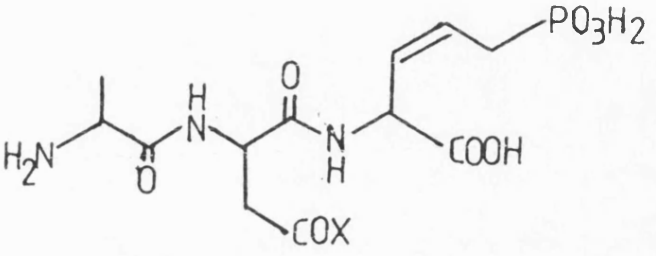
A synthetic strategy was developed to allow an approach to the unambiguous stereorational synthesis of either enantiomer of the unusual unsaturated aminophosphonic acid component (A) of the PLUMBEMYCINS (B) from a carbohydrate precursor. Syntheses of the required chiral synthons (chirons) (C) were achieved by the introduction and controlled rearrangement of unsaturation and functionality in the carbohydrate derivatives. The key synthetic step was envisaged as an O-alkyl lactone ring opening of these suitably functionalised chiral amino lactones, either directly with a nucleophilic phosphorus species or indirectly via initial cleavage to an activated intermediate. These approaches and other methods of ring opening are discussed.

Preliminary investigations into the synthetic potential of the novel chirons were made; particularly, epoxidation of the unsaturated intermediates (C) and (D) and subsequent nucleophilic ring openings were studied. Initial results suggest that the synthons might be useful for the production of polyfunctional aminosugars and amino acids.

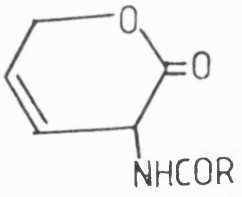
Reviews of asymmetric amino acid synthesis, aminophosphonic acid synthesis and naturally occurring aminophosphonates are presented along with a novel hypothesis regarding the biosynthesis of (A).


PO3H2
H
COOH
NH2

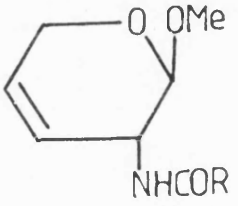
A


PO3H2
H2N
H
N
O
O
N
H
COOH
COX

B (X=-OH,-NH_2)


O
O
NHCOR

C


O
OMe
NHCOR

D

Foreword

Bracketed numerals in the text refer to diagrams of formulae and the arabic superscripts indicate references to the bibliography. The following abbreviations occur in the text.

Ac	Acetyl
Ala	alanyl/alanine
Aq	aqueous
Asn	asparaginyl/asparagine
Asp	aspartyl/aspartic acid
Atm	atmosphere
ATP	adenosine triphosphate
br	broad
BOC	benzyloxycarbonyl
CI	chemical ionisation
COSY	correlation spectroscopy
d	doublet
dd	doublet of doublets
DCM	dichloromethane
DET	diethyltartrate
DIOP	2,3,-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)-butane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
ee	enantiomeric excess
E	electrophile
E I	electron ionisation
Et	ethyl

fod	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione
g	gram
GC	gas chromatography
GC-MS	combined gas chromatography-mass spectroscopy
GTP	guanidine triphosphate
Hrs	hours
Hz	Hertz - the standard unit of frequency
IR	infrared
LDA	lithium diisopropylamide
m	multiplet
M	Mass ion
$m/_z$	mass to charge ratio
Me	methyl
mg	milligram
ml	millilitre
mmol	millimole
mol	moles
mins	minutes
MHz	megahertz
ms	mass spectra
mp	melting point
***m*CPBA**	*meta*-chloroperoxybenzoic acid
N	normality
NA	not assigned
Nu	nucleophile
nm	nanometer
nmr	nuclear magnetic resonance

NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
Pi	inorganic phosphate
Ph	phenyl
ppm	parts per million - chemical shift in nmr
ppt	precipitate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
***p*TSA**	*para*-toluenesulphonic acid
pyr	pyridine
q	quartet
Rf	retention index for thin layer chromatography
reX	recrystallise
r.t.	ambient room temperature
S	singlet
S_N2	bi-molecular nucleophilic substitution/S_N2'-allylic bimolecular nucleophilic substitution
t	triplet
tfc	Tris 3-(trifluoromethylhydroxymethylene)-d-camphorato derivative
tlc	thin layer chromatography
t_{Bu}	tertiary-butyl
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSX	trimethylsilylhalide
TMS	tetramethylsilane

UV	ultraviolet
vol.	an equivalent volume
xylal	3,4-di-*O*-acetylxylal
Δ r	reflux
$[\alpha]_D$	optical rotation, measured at the sodium d-line
δ	chemical shift, from TMS reference
ε max	extinction coefficient
λ	wavelength of UV absorption
υ	frequency of IR absorption

INTRODUCTION

The Asymmetric Synthesis of Amino Acids

Since 1820, when glycine was isolated from gelatin hydrolysis, the catalogue of naturally-occurring amino acids has been extended gradually to encompass the proteinaceous amino acids and then the more exotic species isolated during the search for new antibiotics. When Musso[1] reviewed the field in 1983 upwards of 500 natural amino acids were known; many were highly-functionalised, being unsaturated, tanycyclic, heterocyclic, halogenated, aromatic or containing unusual heteroatoms (sulphur-, selenium- or phosphorus-containing).

This structural variety and the broad spectrum of biological activity encompassed by natural and highly-functionalised synthetic amino acids has led to great interest in their synthesis.[2] Although it is not difficult to produce the common proteinaceous amino acids in industrial quantities by extraction, fermentation or by genetic manipulation of micro-organisms this technique is not always applicable to rarer amino acids, where synthetic methodology allows greater flexibility in production of functionality. However, many synthetic approaches lead to racemic material which must be resolved and re-equilibrated to give good yield of the desired optical isomer (if only one enantiomer is required).

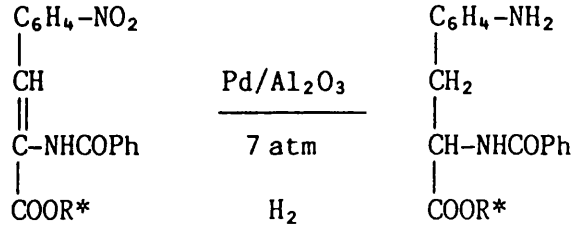
Optical resolution by preferential crystallisation of the amino acid, or a derivative thereof, or by enzymatic asymmetric deprotection of racemic mixtures is readily achieved as is racemisation, either thermally, chemically or enzymatically.

However, asymmetric syntheses of amino acids are of great value as they give unambiguous entry into one (often either) enantiomer

without the need for optical resolution. This goal has been pursued for many years and now 'chiral' enantioselective (and enantiospecific) synthetic procedures have been proven to be in some cases exceptionally flexible. In general, these syntheses rely on either chiral starting materials, chiral auxiliary methodology or the use of a chiral reagent to achieve the aim of creating an optically pure amino acid product.

Asymmetric Approaches to Amino Acids[3]

The first successful attempt at inducing chirality in a synthesis of an α-amino acid was reported by Pedrazzoli[4] in the mid-1950's. He adopted an approach reliant on a diastereoselective catalytic hydrogenation of chiral auxiliary esters of α-benzoylamino cinnamates (see Figure 1).



[R* = (-) menthyl, (-) bornyl]

Figure 1

The optical yields achieved were poor (≤30% e.e); however the principle was established and a further paper by Yamada[5] in 1962 further explored this method with little optical success.

Other approaches based on the hydrogenation of a chiral intermediate were developed.

Hydrogenation of chiral diketopiperazines[3] over platinum oxide catalyst resulted in low optical yield of the freed amino acid (see

Figure 2). A more efficient process (96-99% e.e) has since been published.[6]

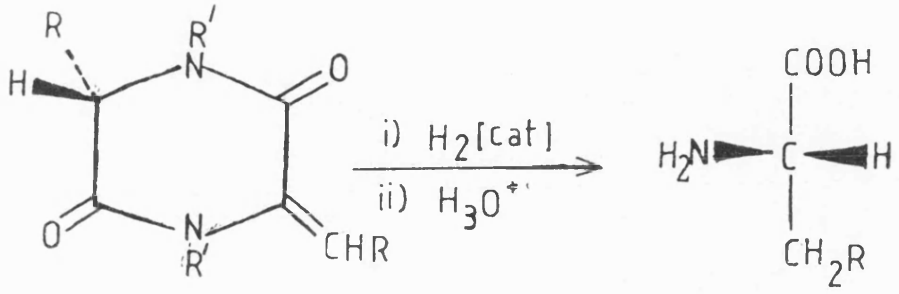


Figure 2

Better asymmetric induction was achieved in the hydrogenation of a different chiral ring,[7] where more steric control is exerted on prochiral face approach to the catalyst surface (see Figure 3).

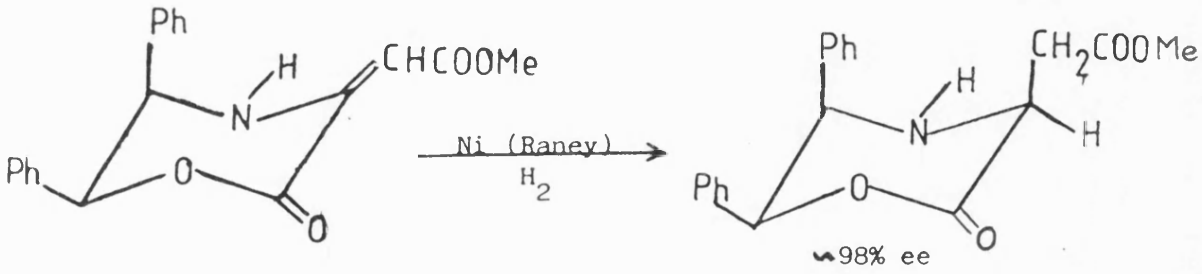
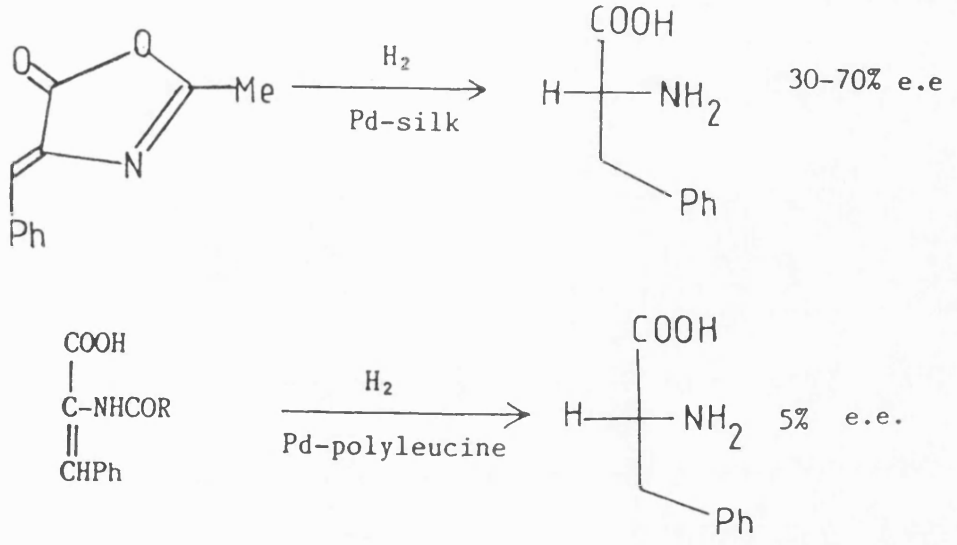


Figure 3

However, one disadvantage of this approach is the sacrifice of the auxiliary. The hydrogenation of chiral α , β-unsaturated amides has also been studied[8] (6-39% e.e).

The hydrogenation of carbon-carbon double bonds has also been studied with chiral catalysts. Originally, heterogeneous systems were studied utilising catalyst metals adsorbed on chiral natural fibres[3] (silk, polypeptides) or utilising Raney-nickel in a chiral solution[3] (alkaline glucose) (see Figure 4).

Figure 4 - Use of Chiral-Phased Heterogeneous Catalysts



However, the many factors responsible for asymmetric induction in these processes and the overall non-uniformity of catalyst environment lead to difficulty.

The obvious solution was the development of uniform chiral hydrogenation catalysts. Wilkinson's discovery of the first efficient homogeneous catalyst[9] $[RhCl(PPh_3)_3]$ and the development of chiral phosphine ligands[10] led to the birth of chiral catalyst species which are capable of highly enantioselective hydrogenations, especially of the enamide precursor of α-amino acids.

The reduction of the imine carbon-nitrogen bond has also been investigated extensively,[11] particularly those processes employing a chiral amine, thus producing a reducible chiral imine intermediate (see Figure 5).

e.g.

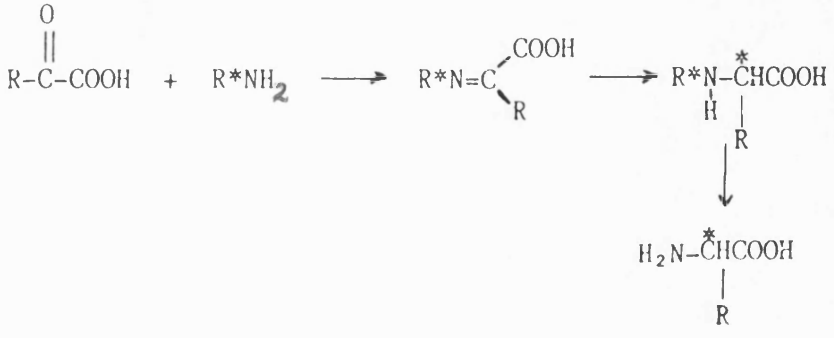


Figure 5

Here R* should be a group that is readily and completely removed under non-racemising conditions.[12]

Again, achiral substrates and chiral catalysts may be considered, though hydrogenations with chiral-phased heterogeneous catalysts give poor asymmetric yield.[3] Also related are the non-enzymatic transformations of α-ketoacids using pyridoxal, which, though essentially biomimetic, proceed with low enantioselectivity[13] (see Figure 6).

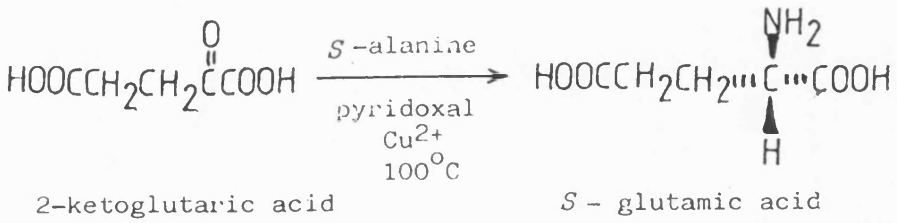


Figure 6

Corey also published[14] a method for the asymmetric synthesis of α-amino acids utilising the reduction of a chiral imine, at the same time elegantly stating, and fulfilling, the requirements for any acceptable chiral auxiliary approach to asymmetric synthesis.

He recognised that:

i) the precursor of the optically-pure target ought to be achiral and possess suitably placed, appropriate functionality for modification (α-keto acid for α-amino acid).

ii) the precursor be constrained with the chiral auxiliary in a ring of minimal size containing the appropriate

reaction site.

iii) the reaction site be tied to the auxiliary by a suitably reactive bond (α-keto acid as hydrazone).

iv) the ring ought to be chiral, containing maximally effective chiral centres.

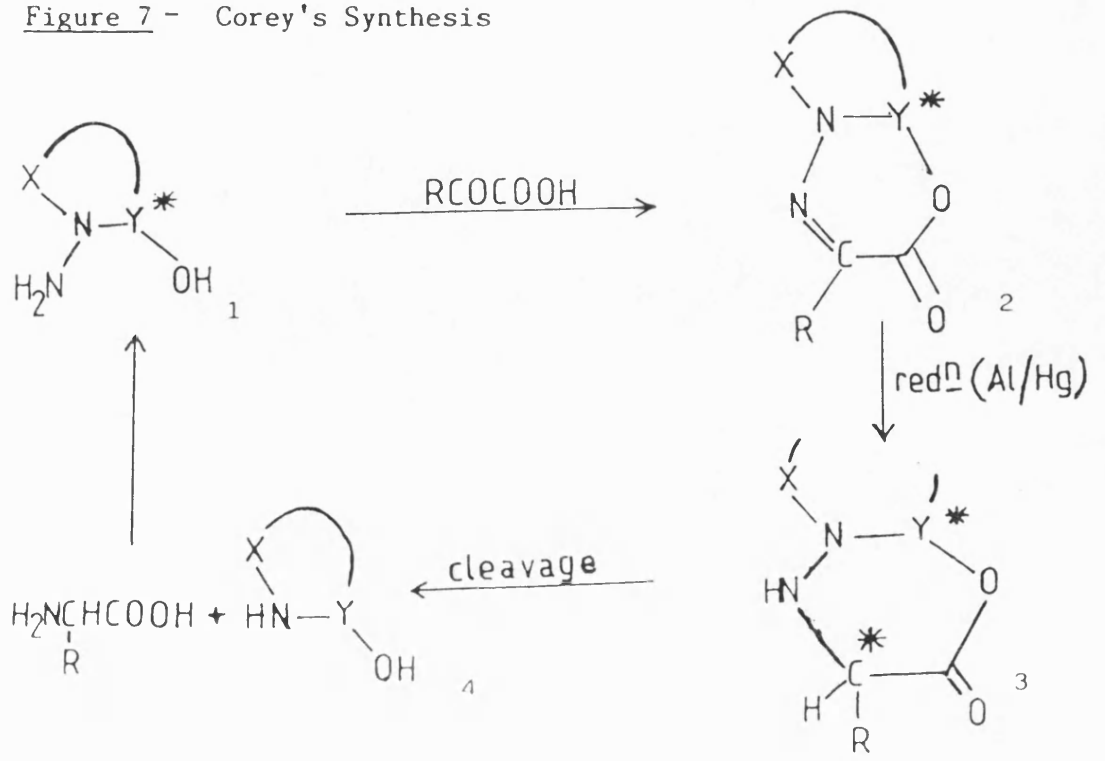
v) the cyclic intermediate be readily reacted to target product and a recoverable fragment of the chiral auxiliary.

vi) the fragment be readily recycled to the original auxiliary.

These conditions should be implicit in any efficient strategy utilising a chiral auxiliary. A further condition, that the other enantiomer of the auxiliary be readily available for enantiocomplementary synthesis, ought to be considered of equal importance. Also, there should be a predictable confidence in the optical outcome with either isomer of the auxiliary.

Corey achieved his synthetic goals with the cycle below (see Figure 7).

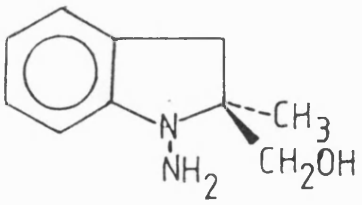
Figure 7 - Corey's Synthesis



The conversion of 3→4 involves *N-N* hydrogenolysis and ester hydrolysis and frees the optically-selected amino-acid and the precursor of the chiral auxiliary. Since *N-N* hydrogenolysis proceeds poorly or not at all if X is attached to *N* by a saturated carbon, but smoothly if X includes an *N*-benzenoid substituent a further structural requirement is thus imposed on the auxiliary.

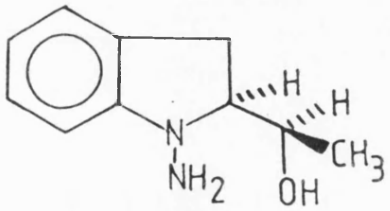
Corey's rationally-designed reagents for the auxiliary, (*R*) and (*S*)-*N*-amino-2-methylhydroxymethylindoline, *A*, and the rationally modified (to have more steric interaction with the reducing centre through the transition state) 1-amino-(*S*)-2[-(*R*)-1-hydroxyethyl] indoline, *B* (see Figure 8) involve lengthy synthesis and a resolution

Figure 8 - Corey's Auxiliaries



A + mirror

> 98% ee



B + mirror

~ 100% ee

step, but fulfill his objectives perfectly. At the time, the elegance of the methodology was unrivalled but it has been little used, being superseded by more accessible systems of α-amino acid construction.

Other reductions of multiply-bonded carbon-nitrogen systems have been utilised in amino acid syntheses, including an asymmetric synthesis from readily-available nitriles employing the chiral reductant, diisocamphenylborane[15] (see Figure 9).

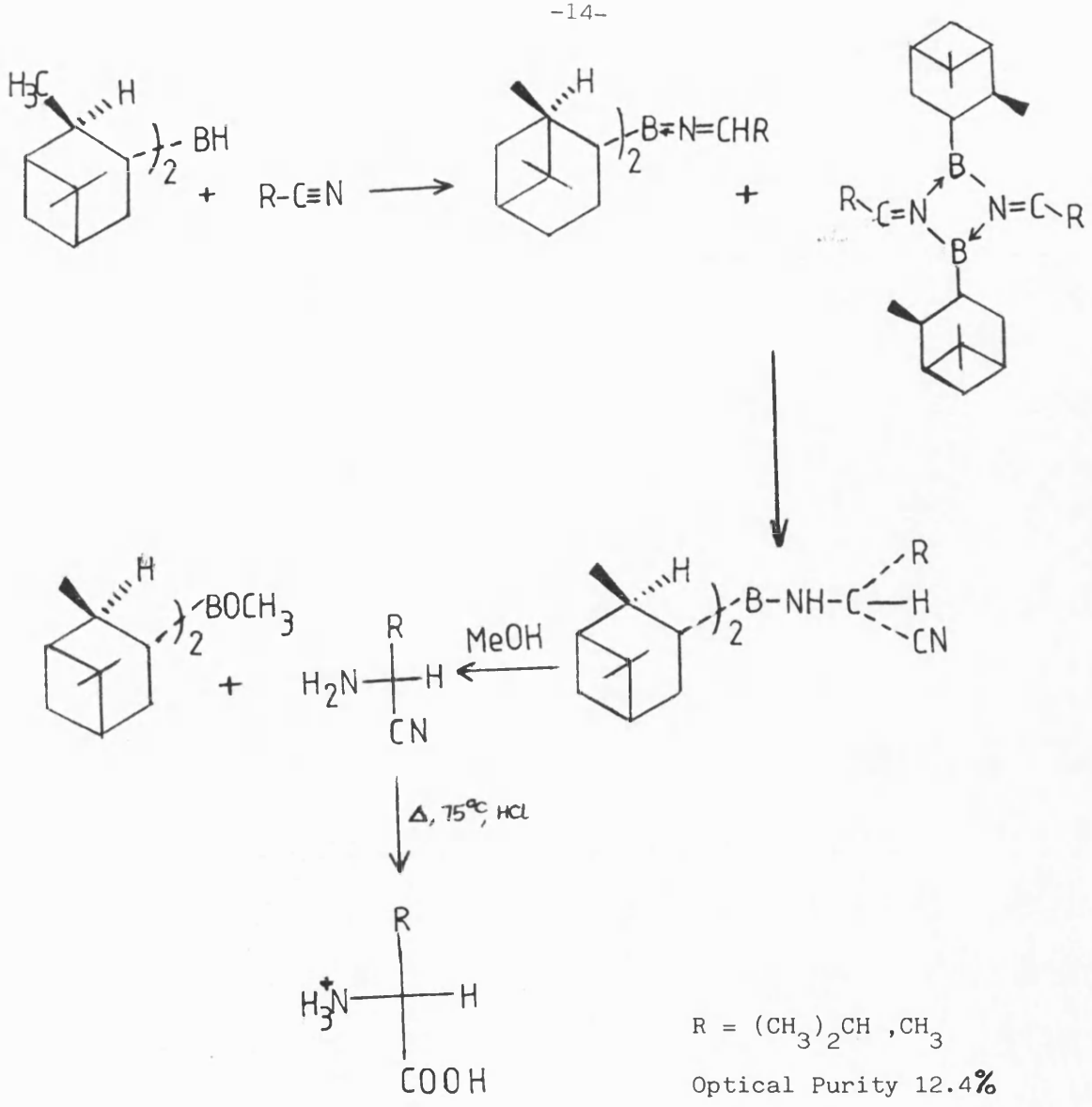
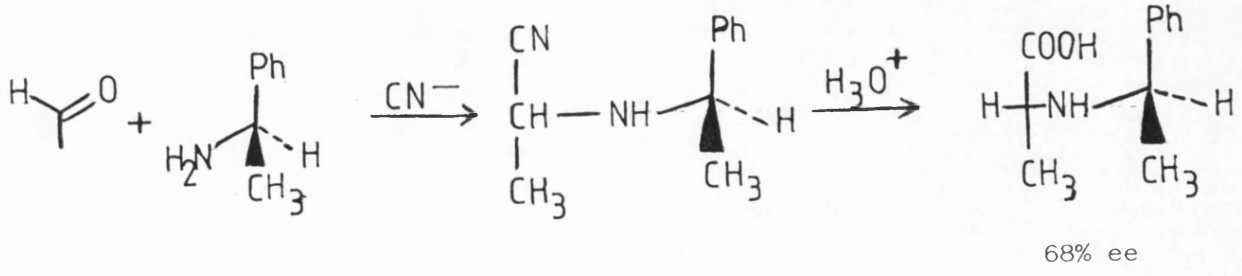


Figure 9

Also reliant on the addition of the elements of HCN to an imine intermediate is the Strecker reaction, chiral versions of which have been published[16] (see Figure 10).

Figure 10 - The Chiral Strecker Reaction



Also reported are asymmetric syntheses realised by addition of nucleophiles to Michael acceptors; here either the nucleophile, the acceptor or a catalyst may be the chiral agent, though asymmetric induction is rather low and few amino acid side-chains are accessible.

e.g.

i) with a chiral nucleophile[17]

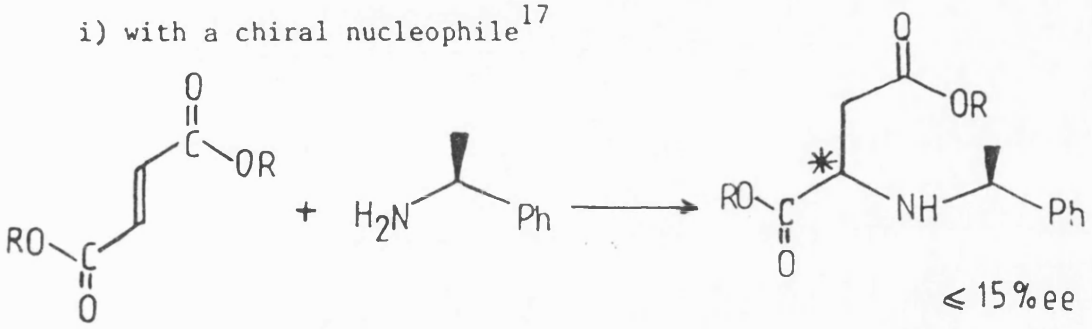


Figure 11

ii) with a chiral substrate[18]

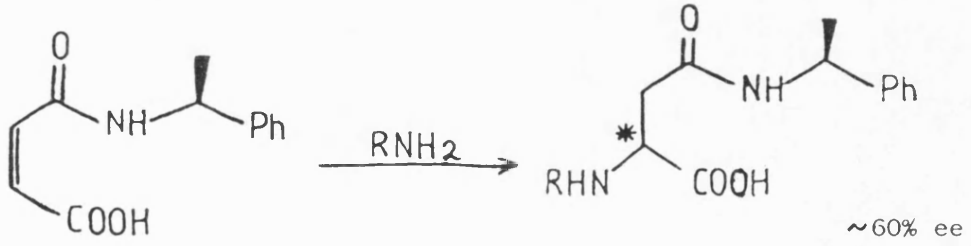


Figure 12

iii) with a chiral catalyst (e.g. enzymatically)[19]

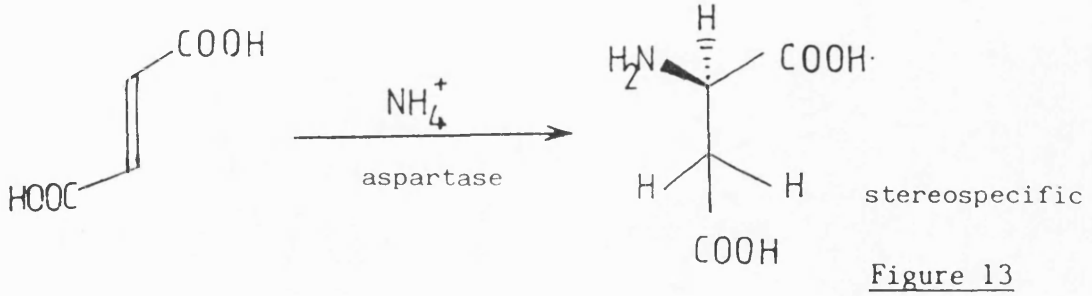
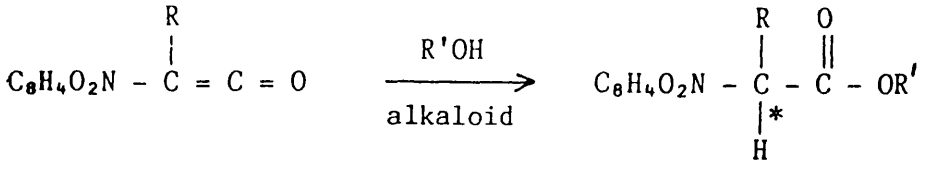


Figure 13

Alkaloid-catalysed additions of achiral alcohols to *N*-phthaloyl alkyl ketene have also been reported[20] (see Figure 14).



[Alkaloid : brucine, acetylquinine] Optical yield : variable

Figure 14

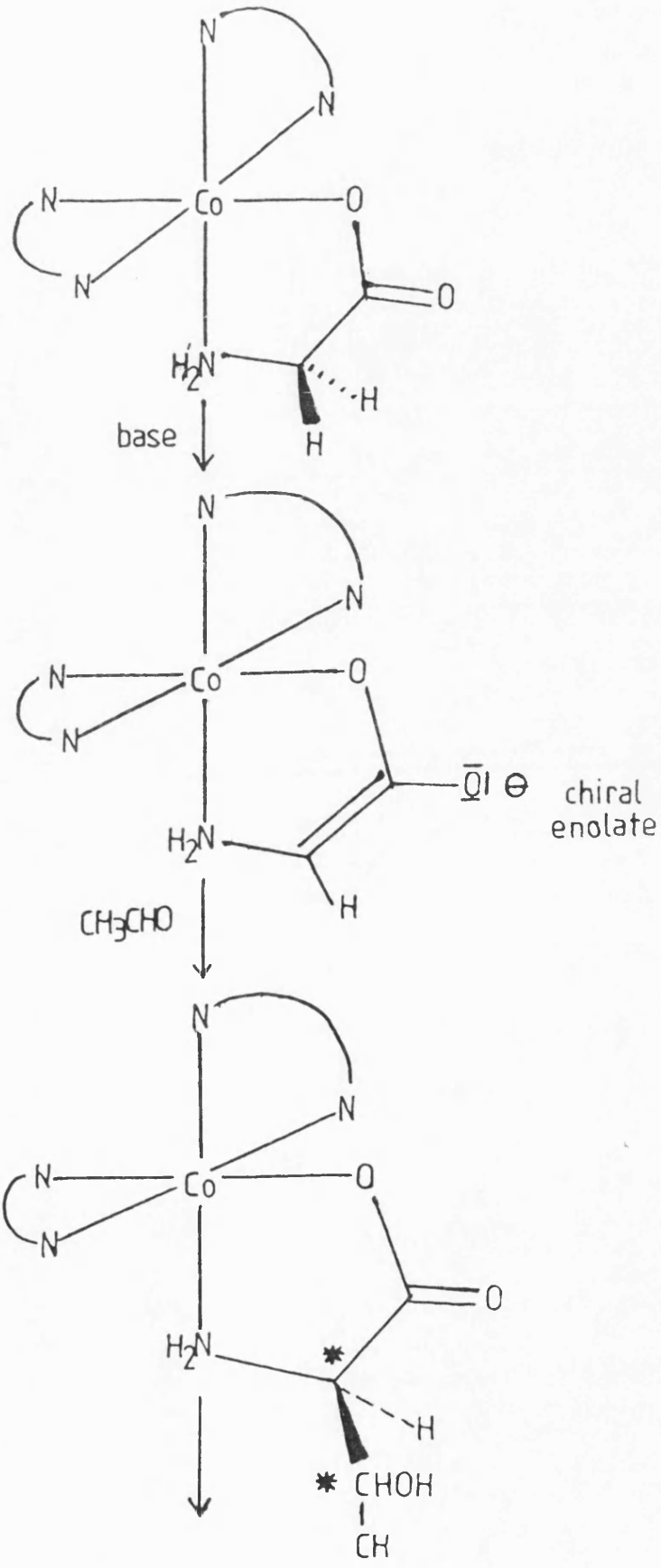
Amino acids have also been synthesised using chiral metal complexes as templates. Early attempts to achieve this explored the possibility of an effective asymmetric synthesis resulting from a reaction that creates a new chiral carbon on a ligand to an intrinsically chiral octahedral complex.[21] For instance, treatment of (-)-glycinato -*bis*-(ethylenediamine)-cobalt-(III)-iodide with acetaldehyde in basic solution causes an asymmetric condensation *via* a chiral enolate (chiral at cobalt) but the product threonine is recovered in low optical yield (see Figure 15).

This enolate approach is of great potential once it is realised that creating a more intimate chiral environment for the enolate would boost the optical yield immensely. This concept has been developed by Seebach, Evans and others, drawing heavily on the tradition of using enolates in 1,3-stereoselection.[23]

Footnote:-

A recent use of a Co^{III} complex,[22] bearing a chiral ligand (R,R-picchxn) to enantio-selectively decarboxylate aminated succinic acid derivatives has been reported. Here the chirality of the decarboxylation is determined by hydrogen-bonding interactions in a secondary complex containing the succinic acid, and proceeds with good enantioselectivity (alanine, for example, has been produced in 78% e.e). Interestingly, the initial chiral complex is regenerated, suggesting the possibility of a catalytic process. However, modifying the sidechain on the amino acid disrupts the H-bonded structure of the complex and optical yields are affected.

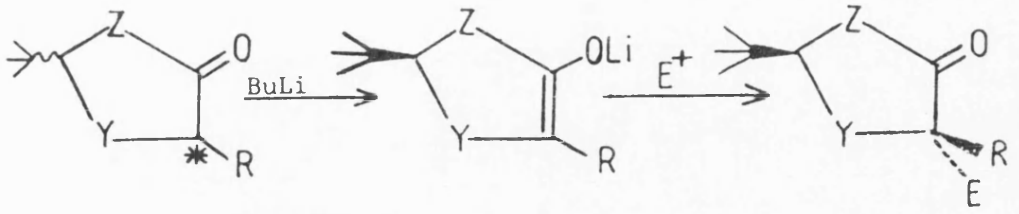
[R,R-picchxn is N,N'-di(2 picolyl)-1R,2S-diaminocyclohexane].



$CH_3\overset{*}{C}H(OH)\overset{*}{C}H(NH_2)COOH$

Figure 15

Seebach's studies[24] have centred around the functionalisation of lithium enolates derived from chiral imidazolidinones and oxazolidinones prepared from amino acids (see Figure 16).



separate diastereomers

Optical yields are generally excellent

A Z = Y = O; R = CH_3, $PhCH_2$, $(CH_3)_2CH$, CH_2COO^-

B Z = O, Y = NCOPh; R = CH_3, $PhCH_2$, $(CH_3)_2CH$, $CH_3SCH_2CH_2$

C Z = NCH , Y = NOPh; R = CH_3, $PhCH_2$, $(CH_3)_2CH$, $CH_3SCH_2CH_2$, C_6H_5

(where E is an alkyl halide, aldehyde, etc.)

Figure 16

When the acetals were prepared from enantiomerically-pure α-heterosubstituted carboxylic acids, it was usually possible to isolate both the *cis*- or the *trans*-isomer, giving ingress to either chiral enolate and the methodology is then almost infinitely extendable (see Figure 17).

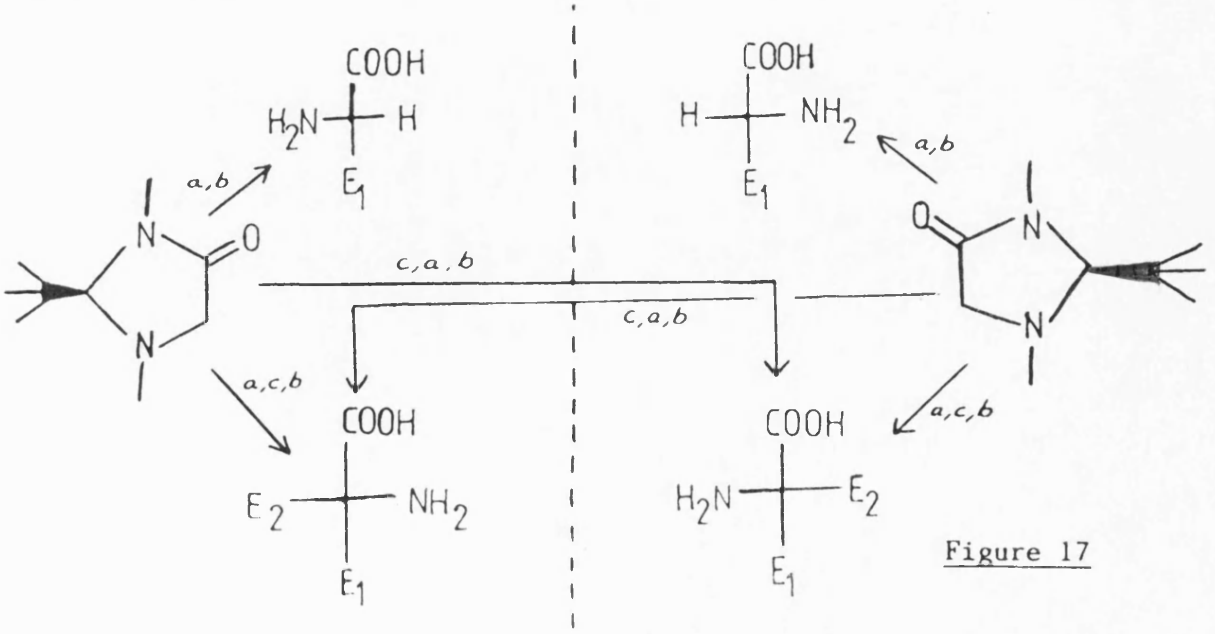


Figure 17

a) addition of E'

b) hydrolytic cleavage

c) addition of E^2

A similar approach has recently been reported by Fadel and Salaun[25] for the synthesis of α-alkylated aspartic acids from amino acids, with self-reproduction of the centre of chirality (see Figure 18).

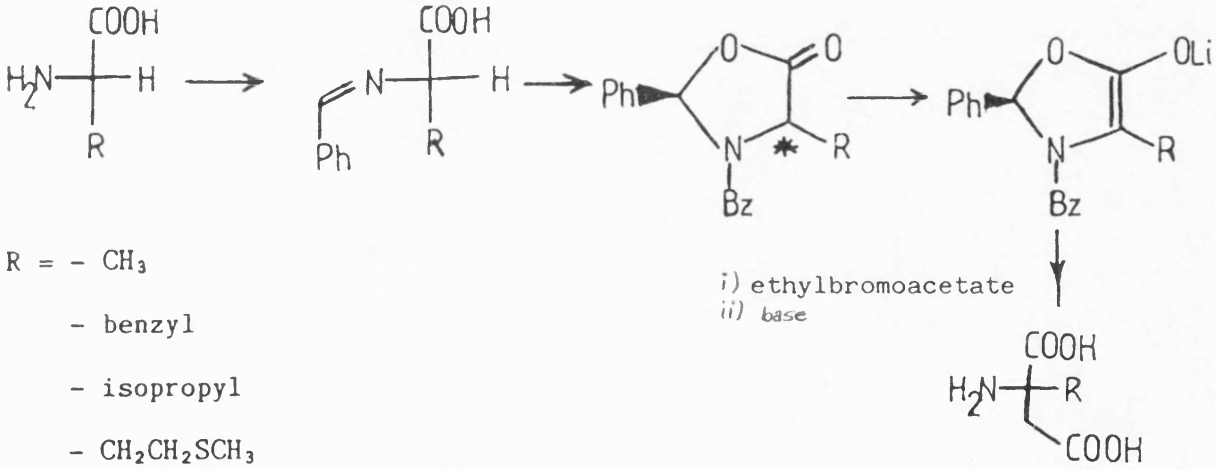
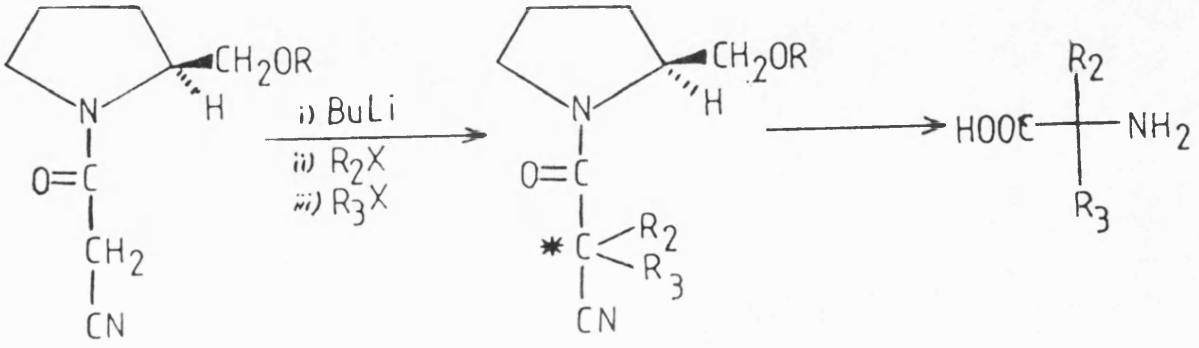


Figure 18

Also applying the idea of generating a chiral enolate were Yamamoto[26] and his group at Osaka, who employed a chiral pyrrolidine as an auxiliary to direct alkylation of a lithium enolate, but with less success in terms of optical yield (see Figure 19).

Figure 19 - Yamamoto's Synthesis



Interestingly, reversing the order of alkylation did not reverse the optical outcome.

Katsuki[27] achieved a highly-diastereoselective alkylation (≥96% e.e) of a glycinate bearing a chiral pyrrolidine (see Figure 20).

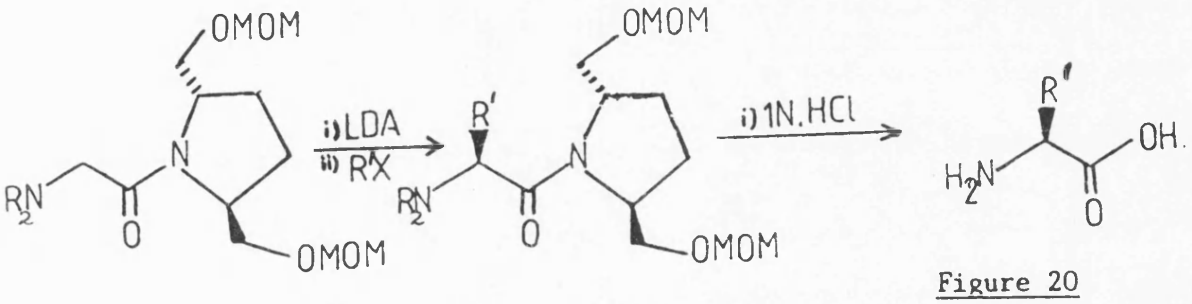


Figure 20

Evans[28] used similar approaches to assemble α-amino acid derivatives asymmetrically:-

i) stereoselective amination of chiral enolates

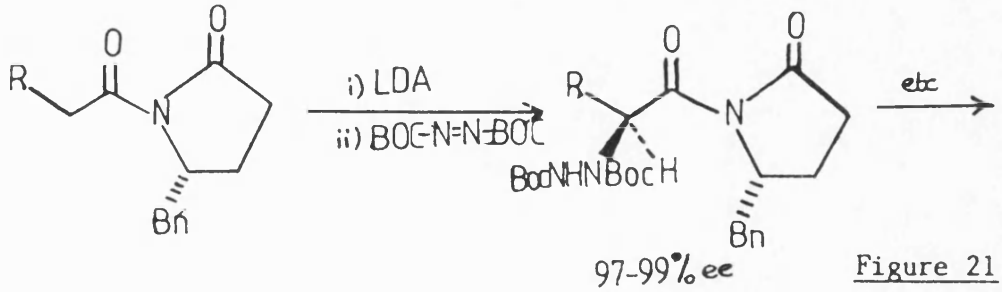


Figure 21

Vederas[29] used an isopropyl-substituted auxiliary in this system, with less success.

ii) Ref[30]

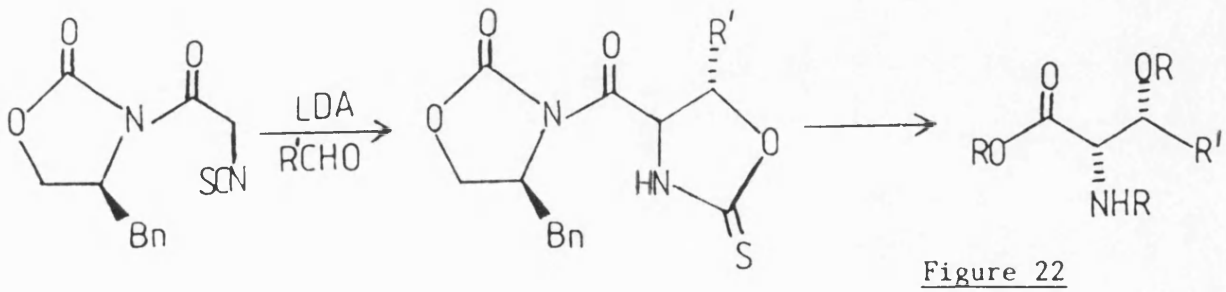


Figure 22

iii) *via* an electrophilic glycinate[31]

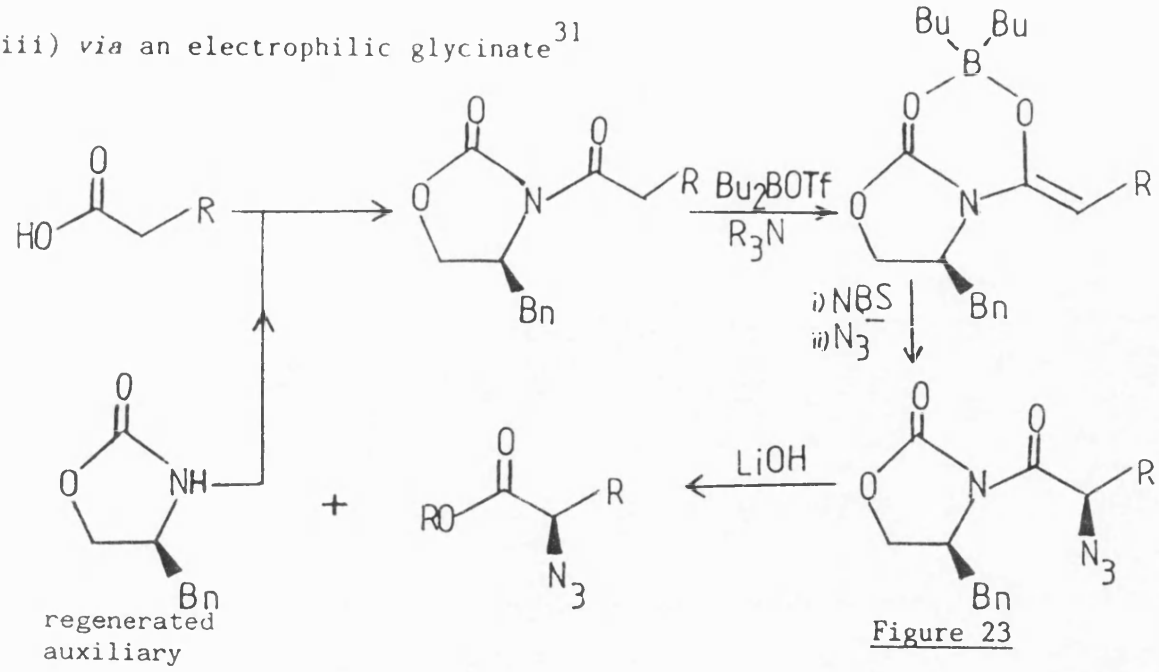
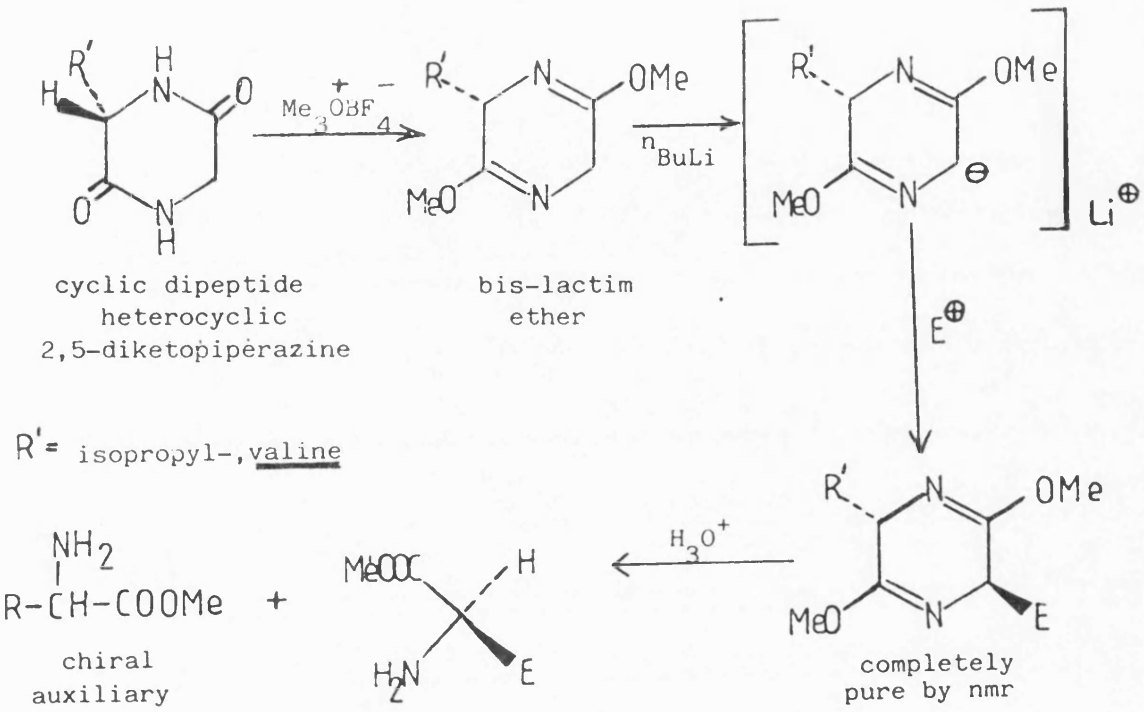


Figure 23

Seebach's method relied upon the generation of a chiral glycinate nucleophile which may be functionalised. This technique has also been adopted by Schollkopf[32] in arguably the most versatile asymmetric approach, in terms of the breadth of application and simplicity of preparation of reagent (see Figure 24). Coupling a prochiral glycine residue with a chiral auxiliary, in this case another amino acid, to establish a heterocyclic unit that is kinetically more acidic α- to the glycyl amine function, allows chirally-directed alkylation; hydrolysis then liberates the newly-functionalised amino acid in a highly optically pure state from the heterocycle, regenerating the auxiliary for recycling, if necessary.

Figure 24 - Schollkopf's Synthesis



This methodology is also applicable to syntheses commencing with racemic alanine rather than glycine, producing chiral α-methylated amino acids with good enantioselectivity.

This methodology has proved to be widely-applicable, generating a variety of highly-functionalised amino acids, in good yield and with good enantioselectivity (see Table 1).

Table 1

Substrate (E)	Functionality in amino acid
ketones /$SOCl_2$, pyr	α-alkenyl
alkyl halides	alkyl
ketones	α-hydroxy
epoxides	β-hydroxy
Michael acceptors	functionalised glutamic acids
$X'-(CH_2)_n-CH_2-X$	cyclopropyl* + larger cycles (see Footnote 1)
glyceraldehydes	polyhydroxylated
Tos-N_3, alkene	cyclopropyl

Substitution of lithium with the more compact titanium enolate increases the diastereoselectivity with respect to the chiral anion and the enantioselectivity of addition to prochiral aldehydes or ketones.[33]

This methodology is readily extendable to the synthesis of ω-phosphonates,# simply by generating a suitable electrophile[34] (see Footnote 2).

*Footnote 1:-

Another route to chiral cyclopropyl amino acids has been developed by Schollkopf, reliant on chiral epoxide ring opening with ^{t}butylisocyanoacetate and reclosure.

R. Gull, V. Schollkopf, Angew Chem. Int. Ed. Engl., 25 (1986) 754.

#Footnote 2:-

A suitable electrophile is not easily envisaged for direct entry to the APPA component of plumbemycin.

However, this strategy is yet more flexible! From the chiral nucleophile may be generated a chiral electrophile,[35] simply by quenching with a positive halide source (C_2Cl_6 or some such), or even a chiral carbene (by producing a diazo complex after quenching with tosylazide).[36]

The electrophilic glycinate so produced undergoes smooth S_N2 reaction; however, the yield is only useful with 'soft' nucleophiles such as thiolates, borohydrides, water or resonance-stabilised anions of carbon-acids, 'harder' nucleophiles leading along alternative reaction pathways.

Other electrophilic chiral glycinates have been developed by Enders and Williams. Enders[37] devised a synthesis of diastereo- and enantio- pure α-amino-γ-oxo-acid esters by reaction of chirally-substituted acyl iminoacetates and chiral enamines (see Figure 25).

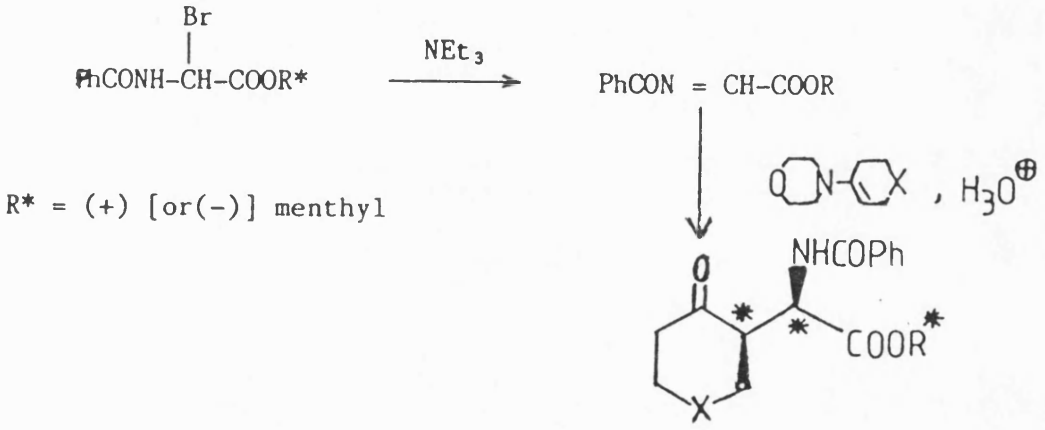
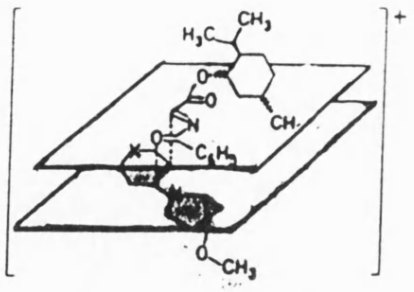


Figure 25

The highly-stereoselective outcome of this reaction may be explained if a Diels-Alder-like transition state is assumed (see Figure 26).



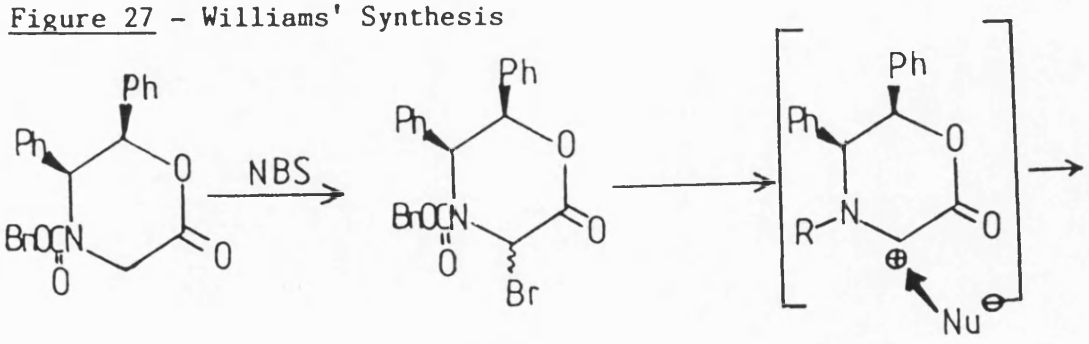
Proposed transition state for the reaction of the chiral acyliminoester with chiral enamines

Figure 26

The addition of chiral auxiliaries to this reaction gives almost complete control of optical outcome. Indeed the use of both a chiral menthyl ester and a chiral enamine (derived from chiral pyrrolidines) is additive so we have both effects complementing each other in the transition state, a case of double asymmetric induction.

The approach developed by Williams[38] again involves the incorporation of a suitably-functionalised glycine residue in a chiral heterocyclic ring (see Figure 27), which allows nucleophilic attack to be directed with high enantioselectivity by steric effects in the ring and, finally, allows hydrogenolysis to proceed to free the newly-functionalised amino acid. However, here the auxiliary is not regenerated in a suitable state for rapid re-use.

Figure 27 - Williams' Synthesis



The auxiliary may be generated from *trans*-stilbene oxide, and requires a classical chemical resolution (with glutamic acid), making the process slightly cumbersome, in the absence of a commercial

supplier of the chirally-pure amino-alcohol auxiliary.

Again, the chiral substrate is best suited for coupling with 'neutral' carbon nucleophiles, such as silyl enol ethers; as the basicity of the nucleophilic species increases debromination becomes a competing process.

The inability of these electrophiles to withstand the attack of 'hard' carbon nucleophiles is rather limiting, and this problem has been little addressed as yet, competing side-reactions of dehalogenation, β-deamination and regiospecificity of nucleophile attack being general disadvantages.[39]

The reaction of α-imino esters with organoboranes overcomes the problems of regioselectivity inherent in this approach.[40]

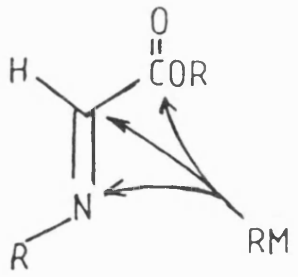


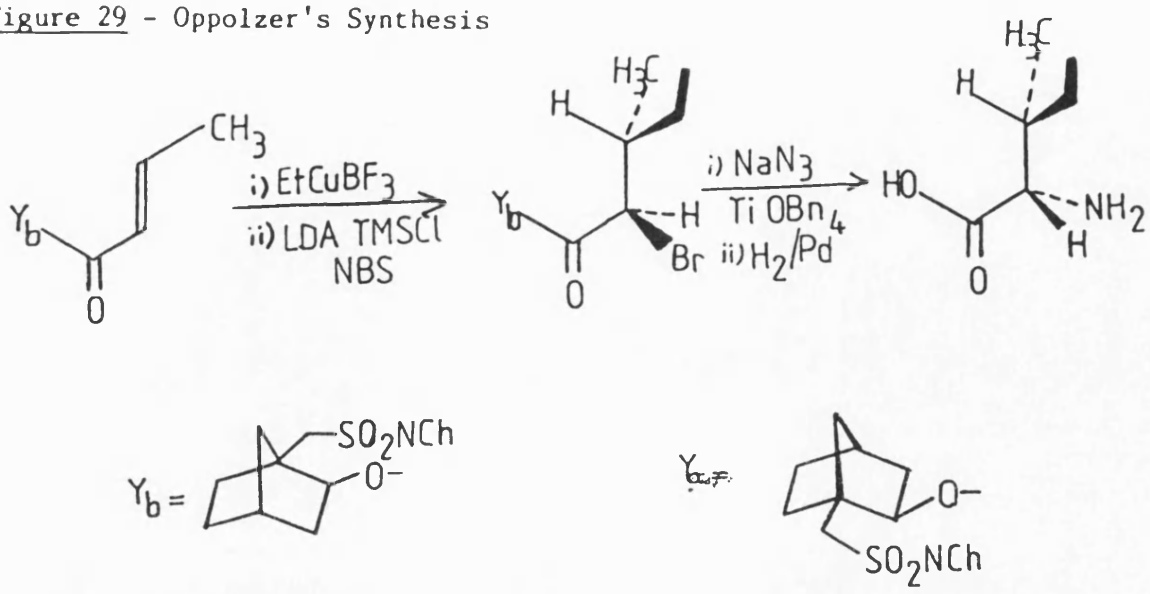
Figure 28

Three possible electrophilic centres are available for nucleophile attack (see Figure 28) but borabicyclo[3.3.1]nonanyl (BBN) alkanes react at the imine carbon, giving the corresponding amino-acids, whereas alkyl-magnesium, -copper or -titanium species reacted at both carbon centres. Thankfully, the reaction also proceeds with high enantioselectivity when the imine is derived from an optically pure amine.

A related system under investigation for the synthesis of optically-pure amino acids in Denmark's[41] group involves the addition of organocerium reagents to species made chiral by employing the SAMP/RAMP hydrazone auxiliary types developed by Enders.

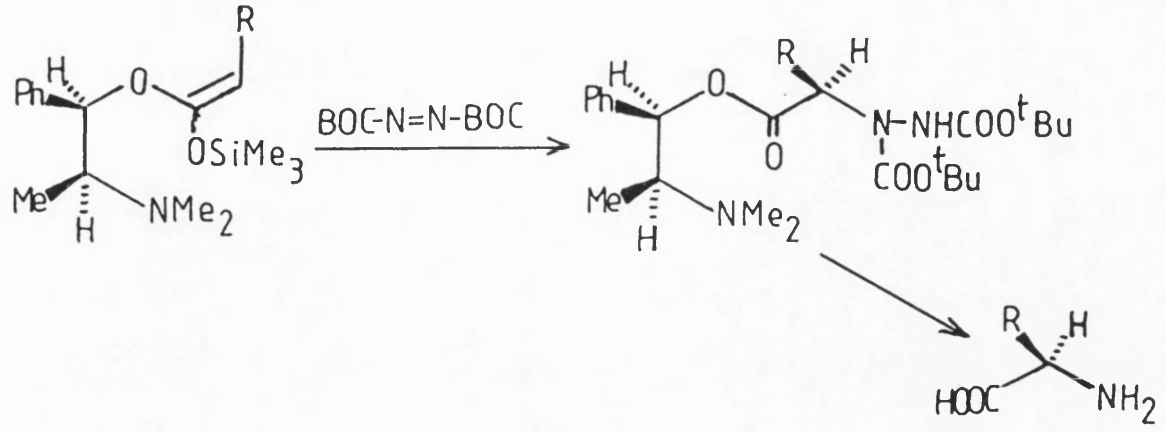
Other chiral electrophilic systems have recently emerged. Oppolzer's[42] applies a more standard auxiliary strategy, employing chiral isobornyl esters to aminate an ester enantioselectively (>94% e e) and in good yield (see Figure 29).

Figure 29 - Oppolzer's Synthesis



Another method of enantioselective amination has been developed by Gennari *et al.*[43] utilising a chirally-modified silyl-enol ether (see Figure 30). This proceeds in good optical (≤80%) yield.

Figure 30 - Gennari's Approach

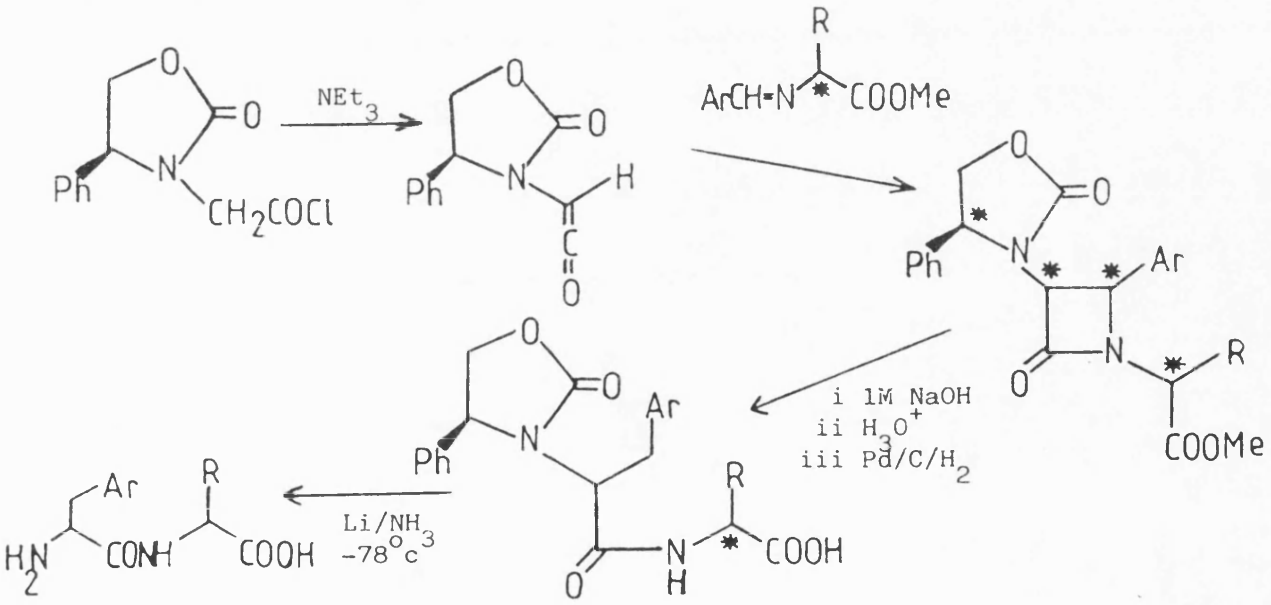


Here the chiral auxiliary is derived from readily available ephedrine (both enantiomers) which is regenerated for recycling.

Enders, in his approach, postulated a transition state resembling

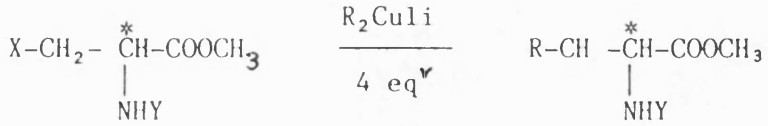
that of a Diels-Alder reaction which was best controlled by both substrates being chiral. Also reliant on this double asymmetric induction, this time of a true cycloaddition process, is the novel route developed by Ojima[44] who produces optically-pure amino acids, di-peptides and their derivatives *via* β-lactams, obtained through [2+2] cycloaddition of homochiral ketenes to homochiral imines (see Figure 31).

Figure 31 - Ojima's Approach



Other synthetic methods rely more heavily on utilisation of the chiral pool, either modifying available amino acids or sugars to produce highly-functionalised amino acids.

Using optically-pure amino acids with an activated sidechain allows displacement with a nucleophile, without racemisation[45] (see Figure 32).

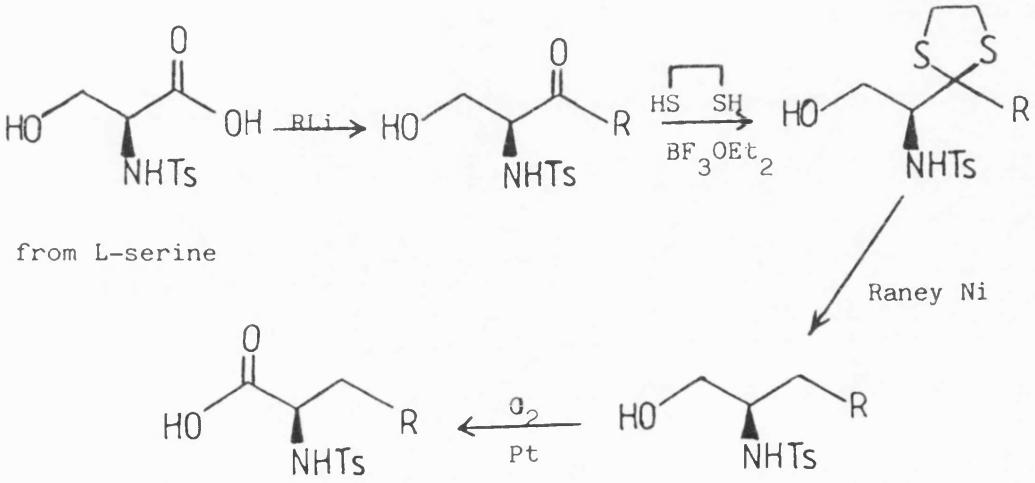


X = halogen, OTs
Y = BOC, Z, Bz

Figure 32

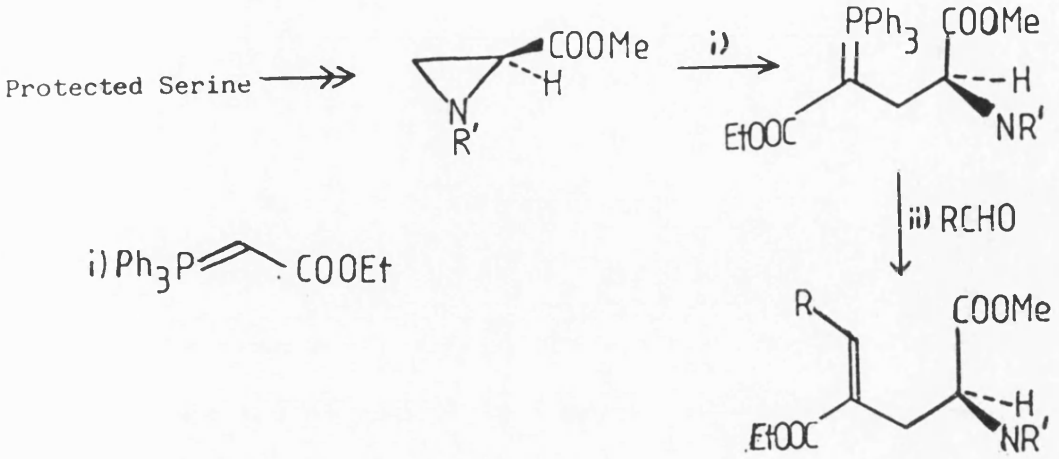
Similarly, Rapoport[46] devised synthetic methodology for D-α-amino acids from L-serine where the chirality is reversed by functionalising the carboxylic acid, reducing to a new sidechain and reoxidising the original serine sidechain to a carboxylic acid (see Figure 33).

Figure 33 - Rapoport's Approach



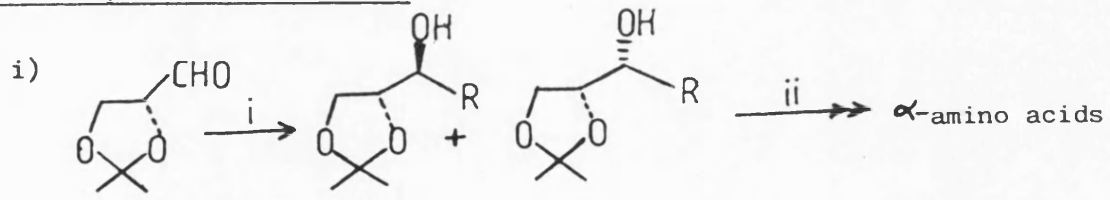
An extremely elegant approach to chiral unsaturated amino acids[47] was recently unveiled by Baldwin,[48] who used an aziridine produced from optically pure serine in a sequence of reactions with a Wittig ylide nucleophile (see Figure 34).

Figure 34 - Baldwin's Approach



Chiral, polyhydroxylated materials may also be modified to amino acids relatively easily, either with complete stereocontrol or with an element of asymmetric induction.

a) with complete stereocontrol

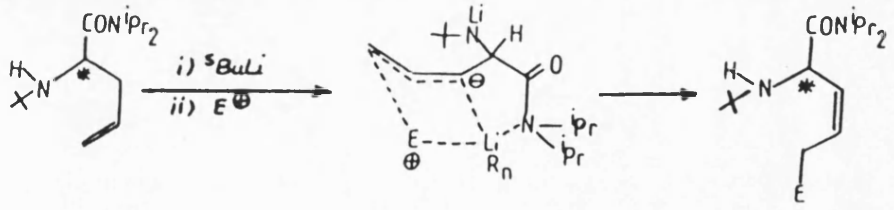


i MR
ii DEAD, PPh_3, phthalimide;etc

Figure 35

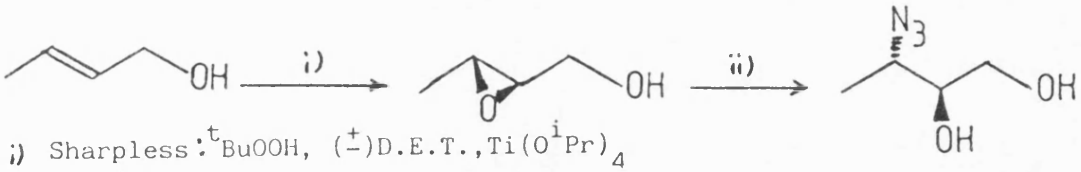
Footnote:-

Prof. Peter Beak (Univ. of Illinois) has revealed in private discussion a route towards w-substituted cis-unsaturated amino-acid derivatives, proceeding via an ortho-lithiated amide which is quenched with a suitable electrophile in an 8-membered ring transition state, thus precluding the formation of a trans-double bond.



The potential of such an approach for a synthesis of APPA should be noted.

ii) synthons available from the Sharpless chiral epoxidation:-



i) Sharpless: $^{t}BuOOH$, $(\pm)$D.E.T., $Ti(O^{i}Pr)_4$

ii) $Ti(O^{i}Pr)_2(N_3)_2$

Figure 36

b) with an element of asymmetric induction from a chiral sugar chain[52]

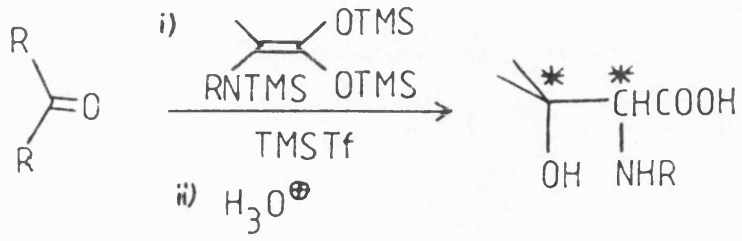
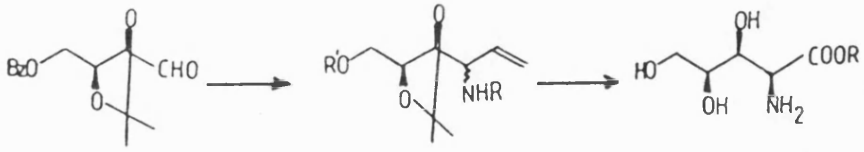


Figure 37

Also worthy of interest is the recent synthesis of polyoxamic acid from tartaric acid,[53] proceeding via Wittig chain extension, Overman rearrangement and oxidative cleavage to the amino acid (see Figure 38).



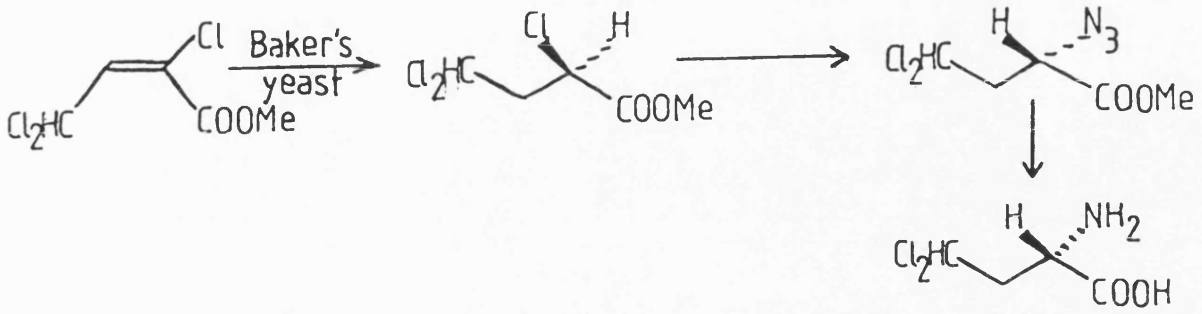
polyoxamic acid

Figure 38

Higher carbohydrates may be used directly, and with complete stereocontrol, when it is realised that a chiral amino lactone so derived is directly equivalent to an amino acid.[54] This methodology is potentially of wide-ranging applicability, but is underdeveloped.

The use of enzymes in organic synthesis for *de novo* generation of chirality is a blossoming field; this technique has recently been applied to amino acid syntheses,[55] utilising Bakers' Yeast to carry

out an enantiospecific reduction of a suitably-functionalised prochiral alkene (see Figure 39).



(65% overall yield, 84-92%ee)

Figure 39

Here, the other alkene geometry allows easy access to the complementary enantiomeric series (60% yield, 97-98% e.e).

The Chemistry and Biochemistry of Phosphonic Acids

INTRODUCTION

Phosphorus, in the form of phosphate esters, occupies a central role in metabolism, being involved in cellular energy-transfer processes (ATP, GTP) and in the genetic materials.

However, the discovery of 'true' natural organophosphates, containing the carbon-phosphorus bond, and the realisation that such phosphonates might be finely-tuned analogues of naturally-occurring phosphates has led to intense interest in the synthesis of a wide range of compounds of this type.[56] The great attraction of phosphonates in this respect is that only one chemical change is required in a highly-functionalised molecule to introduce a highly-specific alteration in that molecule's behaviour under certain circumstances (that is, those dependent on a readily-cleaved phosphate ester linkage) whilst preserving the geometry and leaving the chemistry of the molecule otherwise intact. These two factors combine to give an 'isosteric' surrogate which can be delivered by natural transport systems[57] to the precise point at which biochemistry is to be affected, thus enabling highly-specific control over metabolism.

This simple, rational substitution of bio-inactive functionality for bioactive functionality is a boon for contemporary 'medicinal' chemistry[58] (a discipline which is becoming more refined in its choice of candidates for active compounds) since phosphonates as a general family may possess specific enzymic inhibitory action.

ENZYMIC INHIBITION:-

Drugs are, by definition, chemicals which interfere with

normal life processes at the chemical level, and therefore must be involved in either reversible or irreversible modification of natural biopolymers, whether these are involved in transport phenomena, reception of chemical messages, reproduction, protein synthesis or the chemical transformation of natural biochemicals. Therefore, in order to achieve the goal of rational drug design, it is essential to understand the interaction of biopolymer and natural substrate. It is only with this knowledge that an intelligent choice of inhibitory mechanism may be ascertained.[59]

Essentially, the simplest biopolymers to envisage the inhibition of would be enzymes, as both substrates and products, and hence the transformations involved, are known for many biological processes. Thus enzyme inhibitors or antimetabolites might be efficiently targetted. For instance, if one were to consider the inhibition of a peptidase, a first-stage rationally-designed inhibitor might, for example, simply remove from the natural substrate the key amide bond and replace with an unreactive, but roughly geometrically equivalent, *trans*-double bond (see Figure 40).

Figure 40

More subtle replacements would, however, also have to take account of the lipophilicity and overall electronic structure of the active portion due to their effects on substrate transportation and overall binding capability.

e.g. thioamides as peptidase inhibitors[60] (see Figure 41).

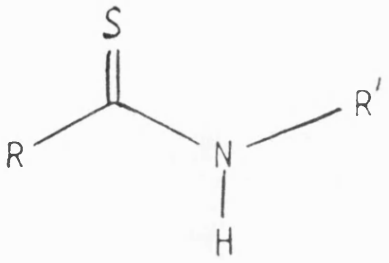
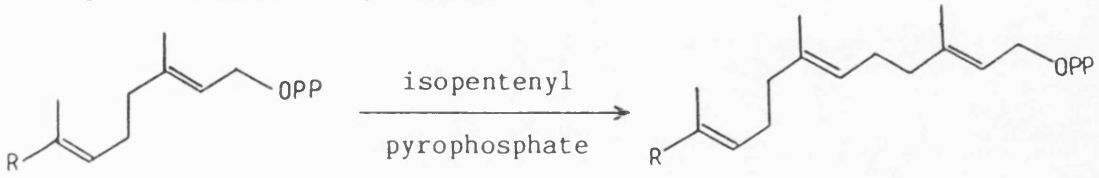


Figure 41

Many enzymatic transformations proceed *via* phosphonylated intermediates (or produce phosphonylated products) where the modification at the phosphate is the crucial biochemical event.

e.g. in steroid biosynthesis



geranyl pyrophosphate — farnesyl pyrophosphate

Figure 42

Thus the phosphonate-phosphate replacement would be a valid choice for an inhibitory mechanism.

phosphate — phosphonate Figure 43

In these phosphonates the methylene unit is the geometrically-correct replacement for the active phosphate oxygen bond. However, the overall lipophilicity (responsible for transport properties) and electronic structure (H-bonding capacity and charge distribution responsible for binding) are both roughly comparable. Thus, isosteric phosphonates might generally be antimetabolites for enzymatic phosphate transformation for more than mere architectural reasons.

In general, enzymic inhibition may proceed by feedback inhibition (loading with a structural analogue of a target product of an enzymatic cascade), or through competitive blocking of the enzymic catalytic site by a substrate which binds with a high affinity compared to the natural substrate (i.e. at a low concentration) but is unmodified (reversible inhibition), or binds covalently to the active site function (irreversible inhibition).

[Enzymatic inhibition by allosteric modification of the active site cannot, at present, be rationally designed.]

Thus a rationally designed enzyme antimetabolite ought to have a structural similarity to the natural substrate or substrates.

Where inhibition depends on substrate modelling it was recognised[61] that the tightest binding (and therefore the highest affinity) of an analogue would occur when the enzyme was encouraged to adopt the intimate 'reaction' geometry without being able to achieve reaction. These reversibly-bound, transition state analogues[62] are the ideal, and isosteric phosphates might require further functional modification to boost affinity and thus maximise binding energy. Again realisation of such inhibitors requires detailed knowledge of enzyme mechanism. If the transition state resembles the product of the process more than the substrate then obviously the inhibitor ought to be designed to mimic this bias.

An enzyme-inhibitory chemical which relies on enzyme action to transform a competitive binder (by normal enzymatic action) to an irreversibly-bound complex is termed a suicide-substrate. The β-lactam antibiotics may be thought of as belonging to this category.

When the enzyme to be inhibited chemically combines two substrates, knowledge of the catalysed reaction mechanism might allow definition of an analogue which mimics the reaction transition state.

This rationally-designed multisubstrate inhibitor has the benefit of having a large affinity for the active site compared to the natural substrates (i.e. is almost non-competitive) and thus ought to be active at low concentration. This multisubstrate inhibition is an important concept as here the substrates are too simple to confer enzymic specificity on any inhibitor based on substrate structure, and inhibition should strive for specificity.

Phosphonates have again been used for this type of enzyme inhibition:-[63]

N-(phosphonoacetyl)-L-aspartate (PALA)[63] has been developed as a potent inhibitor of uridine biosynthesis (see Figure 44).

enzymic process:-

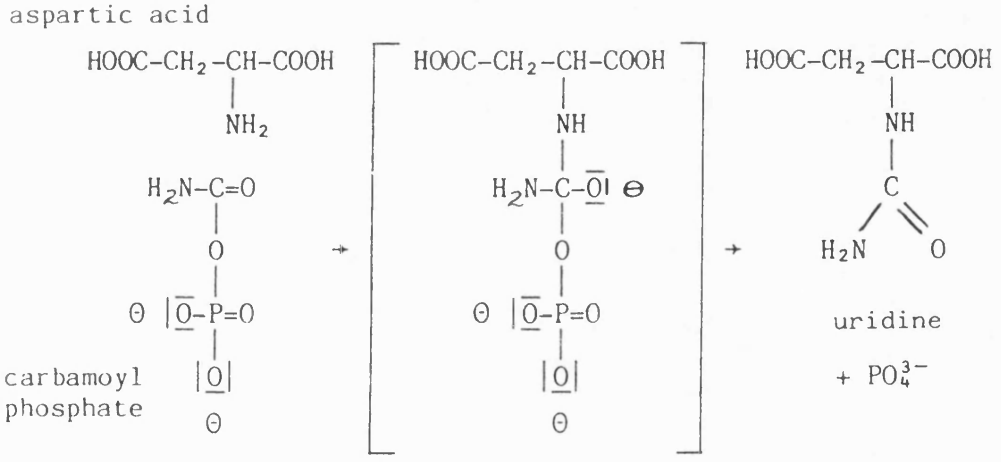


Figure 44

PALA as transition-state multisubstrate inhibitor (see Figure 45):-

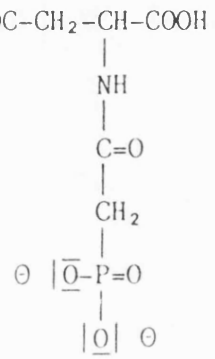


Figure 45

PALA is bound to aspartate transcarbamylase one thousand times more strongly than carbamoyl phosphate.

Recently biochemical research has provided several novel phosphonates which display antibiotic properties. Amongst these are the aminophosphonic acids which are nicely illustrative of the types of rational inhibitory mechanisms referred to above.

Aminophosphonic Acids of Biological Interest

A rather obvious substitution to be made in a group of eminently biologically-active compounds would be a 'first-stage' replacement of the carboxyl group of the α-amino acids with a phosphonic acid grouping.[64*] Here we are simply implying the change of one acidic functionality for another, with no regard for overall acidity, electronic or steric considerations. However, in terms of drug development this replacement has proved valuable, as phosphonamide bonds, when compared to the natural peptide bond, are much more stable to hydrolysis,[65] and hence small 'peptides' incorporating such a linkage are useful for providing peptidic material with enhanced lifetime but retaining the transport characteristics of the natural material.[66]

Even more importantly, in terms of rationalising the design of enzyme inhibitors, Bartlett described a strategy for inhibition of carboxypeptidase,[67] wherein the endophosphonamide linkage could be considered as a transition state surrogate for the tetrahedral intermediate invoked during the enzymic hydrolysis of the peptide link.

*Footnote:-

A second-stage, slightly more sophisticated comparison of the possible 1-aminoalkyl phosphorous acid types with their carboxylic acid analogs suggest that the closest parallel in properties would be with a monobasic phosphorous acid with a small second substituent.

Bartlett extended the analogy to the design of inhibitors for thermolysin[68] and serine proteases.

Other workers have studied similar systems as inhibitors of encephalinase[70] and other peptidases.[71]

Phosphonamidates have also received attention as potential angiotensin converting hormone (ACE) inhibitors and antihypertensives[72] (see Figure 46).

Figure 46

With such activity in mind many α-aminophosphonic acid analogues have been prepared synthetically,[73] often in racemic form (see Figure 47).

Figure 47:- The α-aminophosphonic acid analogy.

Methods of synthesis of α-aminophosphonic acids (and α-aminophosphinic acids) have been extensively studied[74] and reviewed, but little attention has been paid to their chiral synthesis, resolution being generally preferred.

A Brief Overview of the Synthesis of α-aminophosphonic acids and α-aminophosphinic acids:-

i) Addition of Phosphorus Nucleophiles to Carbon-Nitrogen Double Bonds:-

Numerous examples of this type of procedure have been reported in the literature, and a range of substrates containing carbon-nitrogen double bonds may be used.

a: to imines

Here the imine may be formed as the active intermediate of an *in situ* Mannich-type procedure[75] or pregenerated.[76]

e.g. Mannich type procedure:-

$$R_2O_3PH + R'R''CO + NH_3 \rightarrow (RO)_2P(O)CR'R''NH_2$$

This method is limited, as primary amines treated with one equivalent of formaldehyde and phosphorous acid yield mixtures of mono- and di-phosphonic acids. It was noted that generally these reactions proceeded better if the imine was preformed.

Addition to a pre-generated imine:-

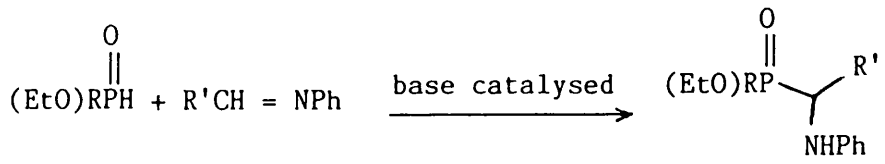


Figure 48

Imines derived from chiral amines[77] or from chiral aldehydes[78] (carbohydrates) allow chiral aminophosphorous acids to be produced by asymmetric induction (see Figure 49 overleaf).

The reactions of 1,3,5-tribenzylhexahydrotriazine and pyrroline trimer with dialkylphosphites are also thought to proceed *via* imine intermediates.[79]

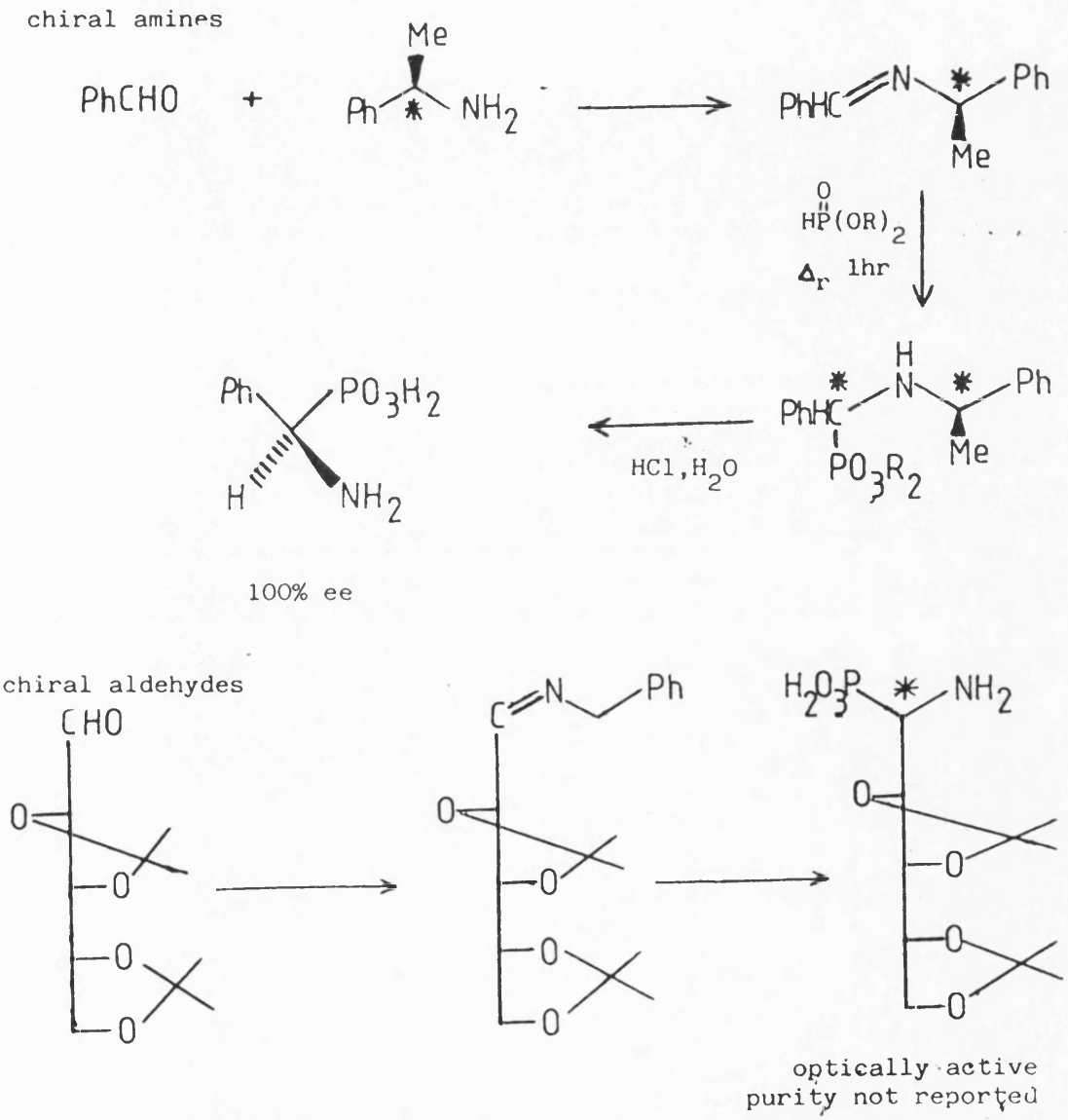

chiral amines
PhCHO
Me
Ph
NH2
PhHC
N
Ph
Me
O
HP(OR)2
Δr 1hr
H
PhHC
PO3R2
HCl, H2O
Ph
PO3H2
H
NH2
100% ee
chiral aldehydes
CHO
O
C
N
Ph
H2O3P
NH2
optically active
purity not reported

Figure 49

Other methods of preparation of α-aminophosphonic acids and α-aminophosphinic acids which proceed *via* an imine-like intermediate, include

i)

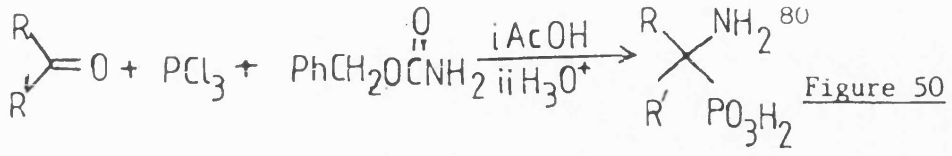


Figure 50

ii)

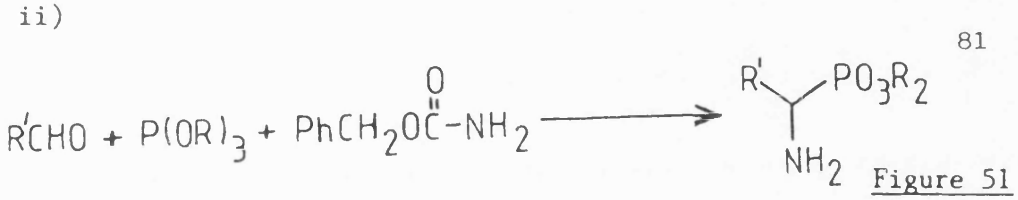


Figure 51

iii)

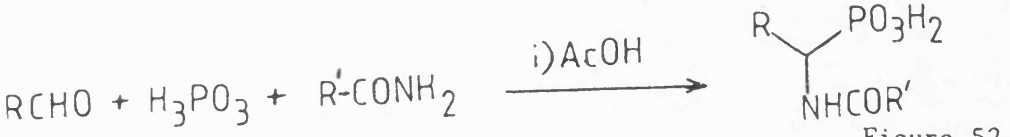


Figure 52

iv)

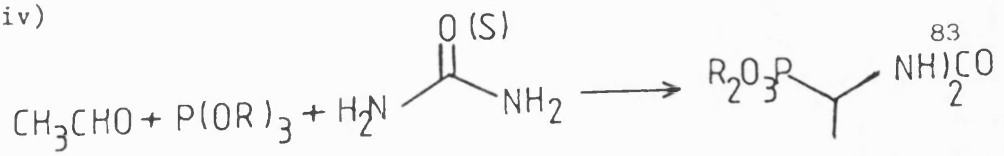
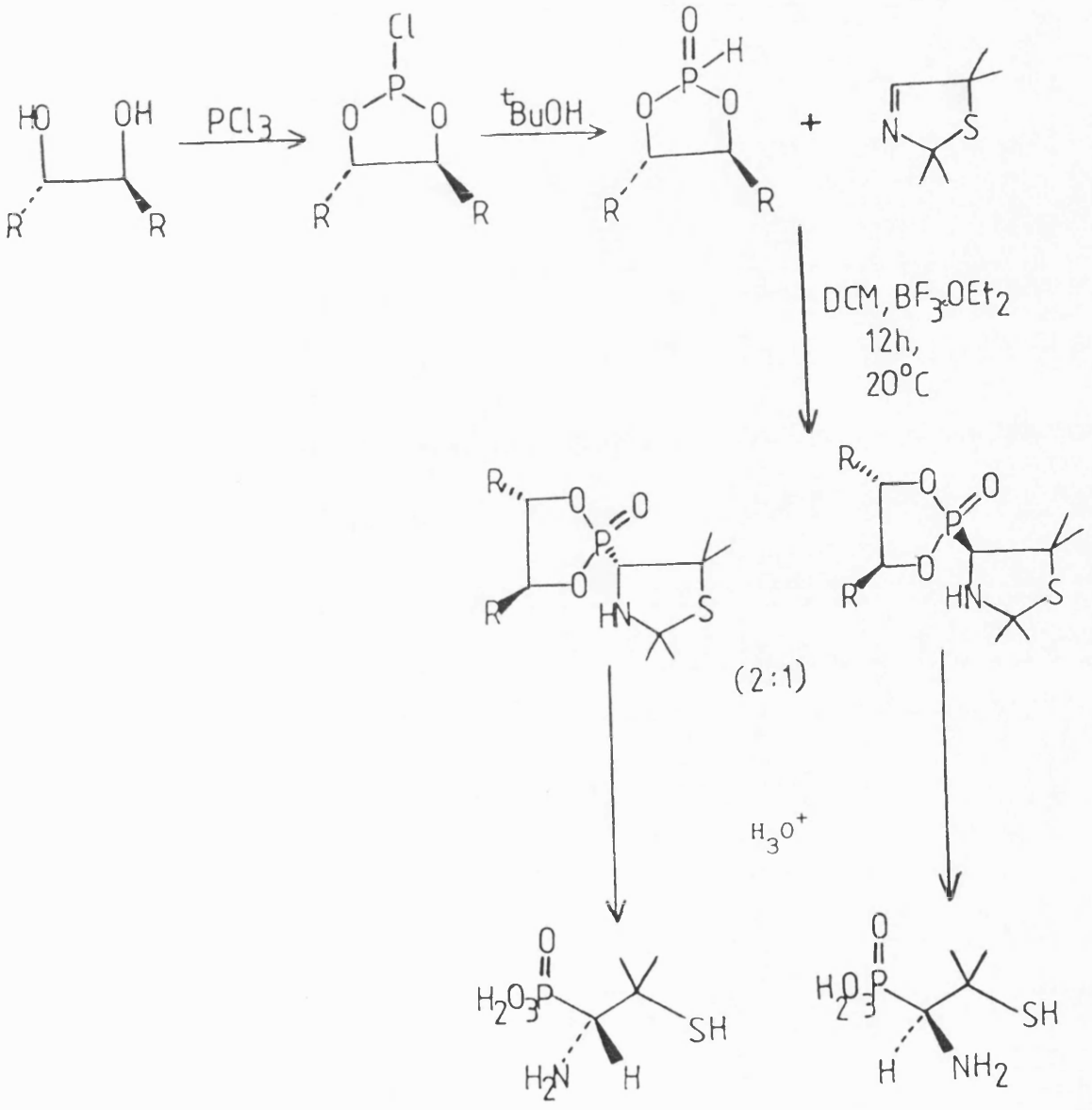


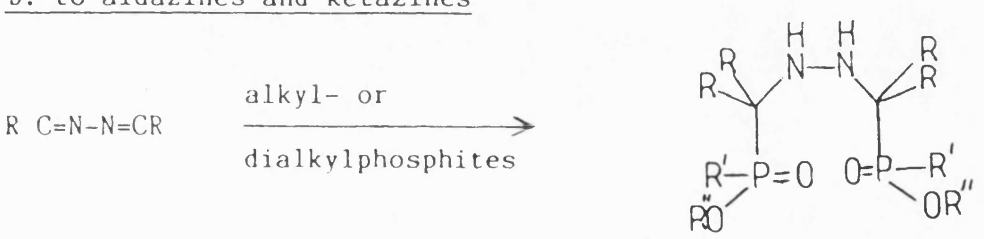
Figure 53

A chiral synthetic approach has been developed by Schollkopf[84] which relies on the approach of a 'chiral' phosphorus nucleophile to an imine, 2,5-dihydro-2,2,5,5-tetramethylthiazole, allowing simple separation of the diastereomeric adducts prior to deprotection of the phosphorous acid *and* the heterocycle with aqueous acid (see Figure 54). This is an exceptionally elegant approach to phosphonic acid analogues of penicillamine.

Figure 54 - Schollkopf's Synthesis of Analogues of Penicillamine.



b: to aldazines and ketazines[85]



[R = Ph, R' = alkyl, alkoxy-, R'' = alkyl]

Figure 55

c: to isothioacetamides[86]

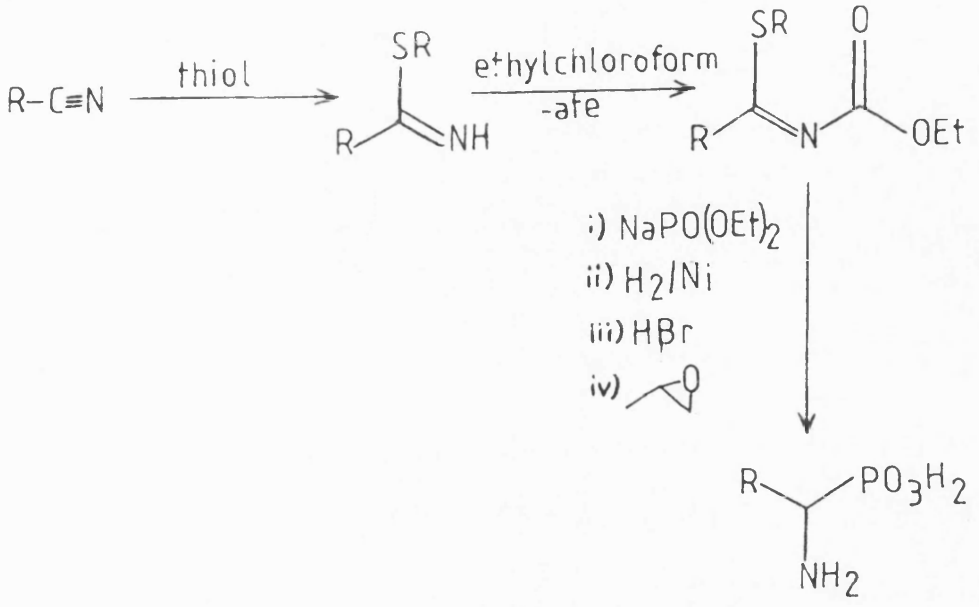
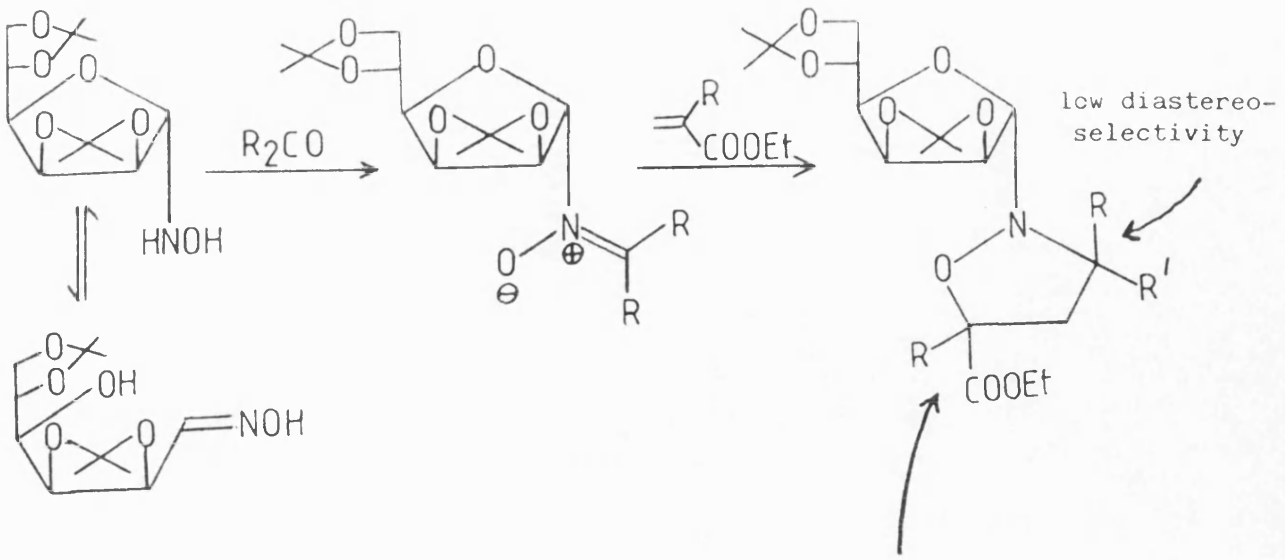


Figure 56

d: to nitrones

The addition of dialkylphosphites to nitrones has been used by Vasella[87] in the asymmetric synthesis of several aminophosphonic acids.

N -glycosyl nitrones are easily produced from carbohydrates, and due to the proximity of the nitrone to the chiral carbohydrate moiety asymmetric induction is evident in nitrone reactivity (both in 1,3-dipolar cycloaddition and in the addition of various nucleophiles) (see Figure 57).



diastereoselectivity

observed at this centre

- conformational analysis

Figure 57

The diastereoselectivity in nitrone reaction has been rationalised on the basis of a stereoelectronic effect in the transition state.[88] This effect is essentially an extended anomeric effect with an alignment of lone pairs in space giving the lowest energy transition state (and an increase of nitrone reactivity by the α-effect). Thus this kinetic anomeric effect predicts the reaction geometry of the nitrone.

Since the diastereoselectivity of reaction increases with increasing nitrone substitution it would appear that the sterically less-congested '^{O}endo' conformation reacts preferentially (see Figure 58).

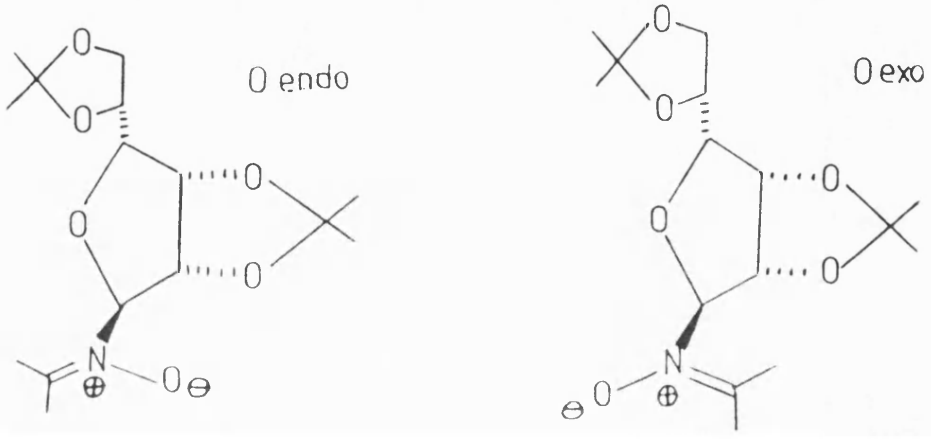


Figure 58

Two more factors determine the asymmetric induction:-

i) the direction of approach of the dipolarophile - controlled by stereoelectronic effects

ii) the exo-endo orientation of its substituents - controlled by steric effects.

Extension of this nitrone diastereoselection to the syntheses of α-amino acids and α-aminophosphonic acids has been achieved (see Figure 59).

by cycloaddition:-

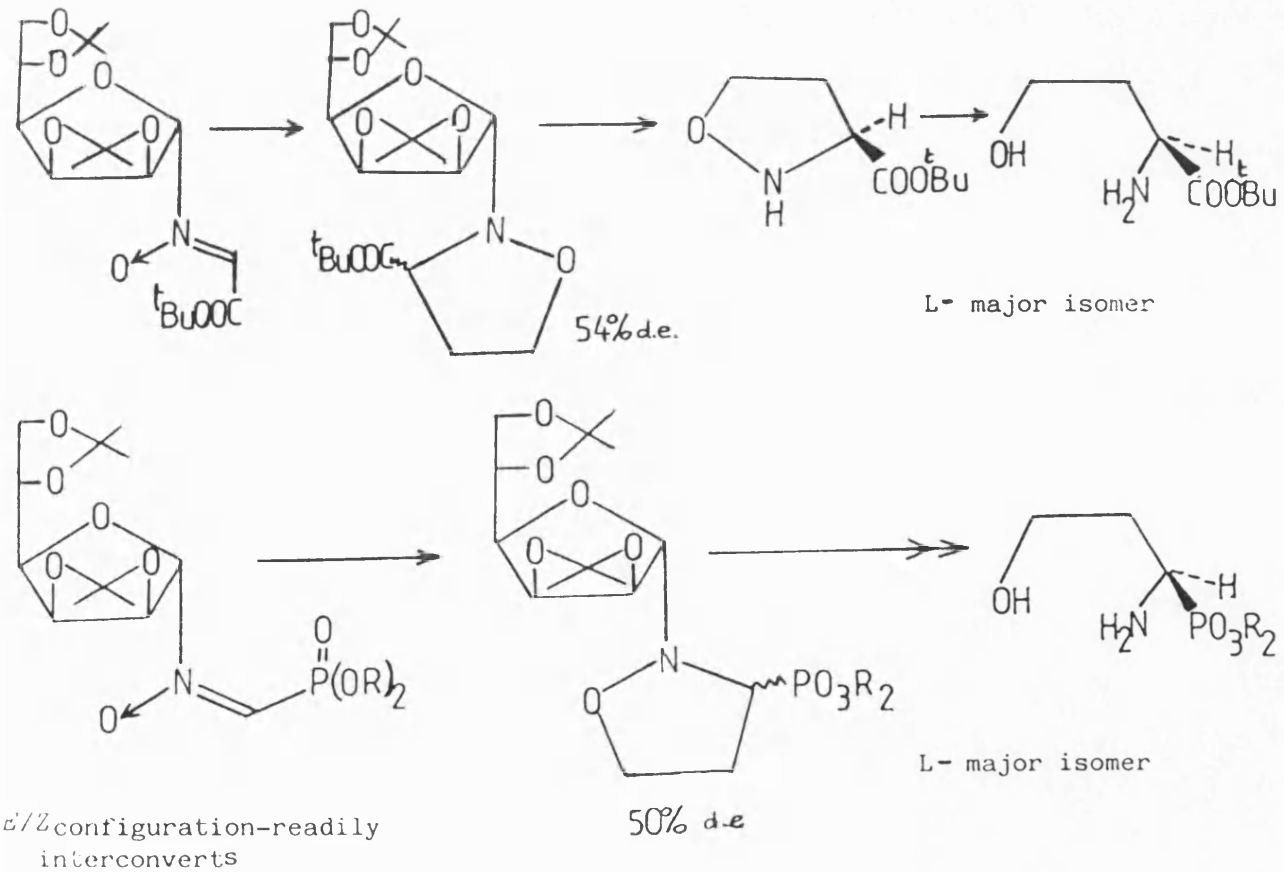


Figure 59

The relatively low diastereoselectivity is due to the ready inter-conversion of nitrone geometry; use of configurationally homogeneous

nitrones and nucleophilic additions of phosphorus nucleophiles (which depend critically on stereo- and stereoelectronic effects as well as being complicated by chelation and charge-dipole effects) allowed diastereoselectivity of 90% or above, with L-absolute configuration (see Figure 60).

The reverse absolute configuration can be approached by switching to another carbohydrate precursor or may be controlled by addition of catalytic quantities of Lewis acid ($ZnCl_2$) or protons, which by interfering with reaction-controlling electronic effects have marked effects on chiral outcome.

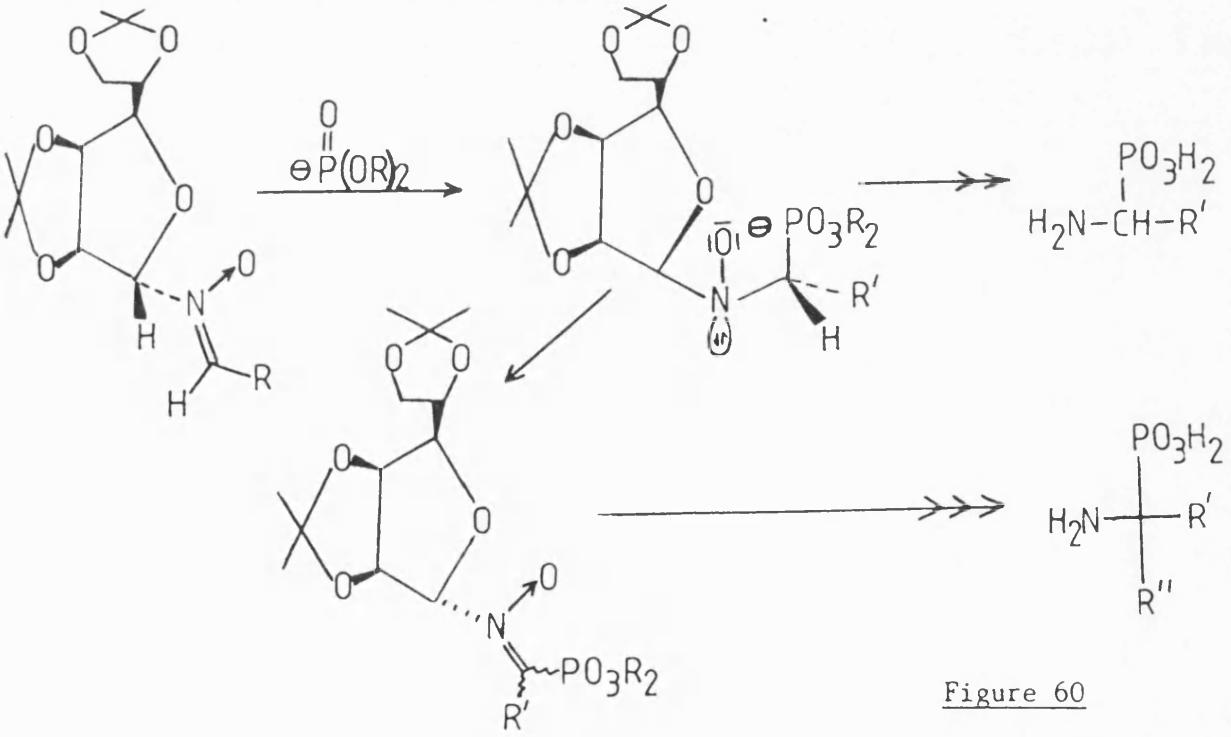


Figure 60

iii) Procedures which occur *via* a Michaelis-Becker or Arbusov transformation

Arbusov

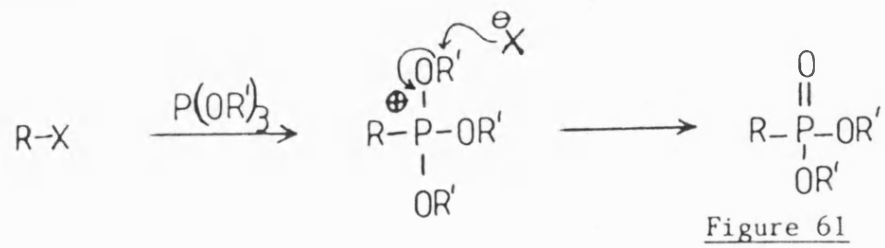


Figure 61

The Michaelis-Becker reaction is supplementary to the Arbusov reaction in that the phosphorus nucleophile may be a dialkylphosphite, an alkylphosphonite or a phosphonite anion.

The phosphorus nucleophile may react with alkyl halides, acyl halides, Michael acceptors (α,β-unsaturated carbonyls), isothiocyanates, aziridines and acyliminium species:-

a) with alkyl halides[89]

e.g.

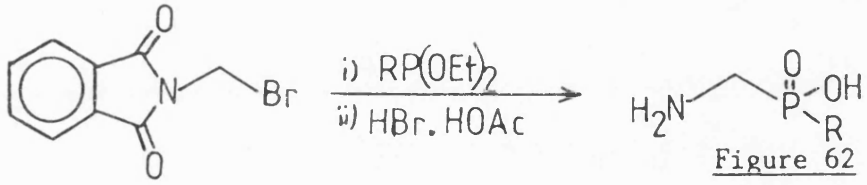
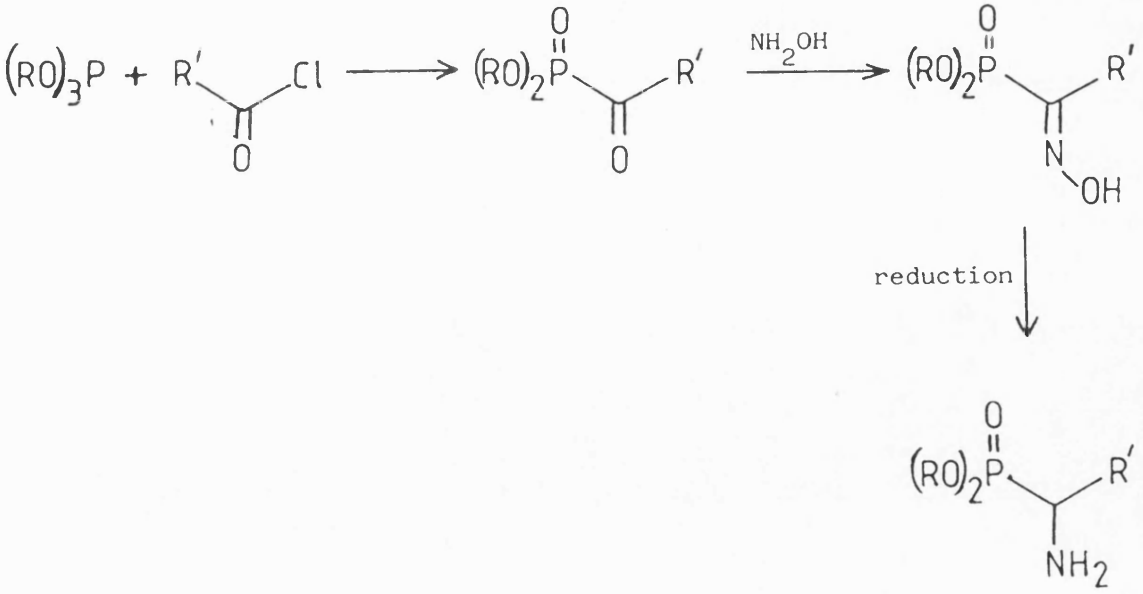


Figure 62

The synthesis of α-aminophosphonic acids depends upon the availability of suitably-functionalised halides.

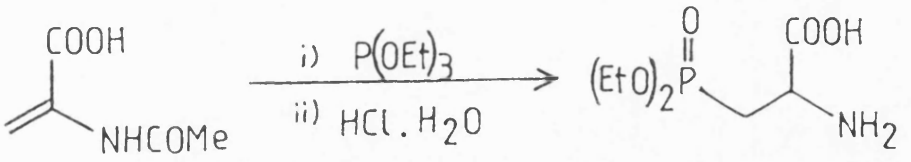
b) with acyl halides[90]

e.g.



c) with Michael Acceptors[91]

i)



ii)

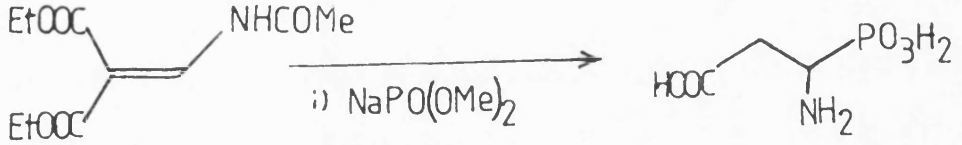


Figure 64

d) with isothiocyanates[92]

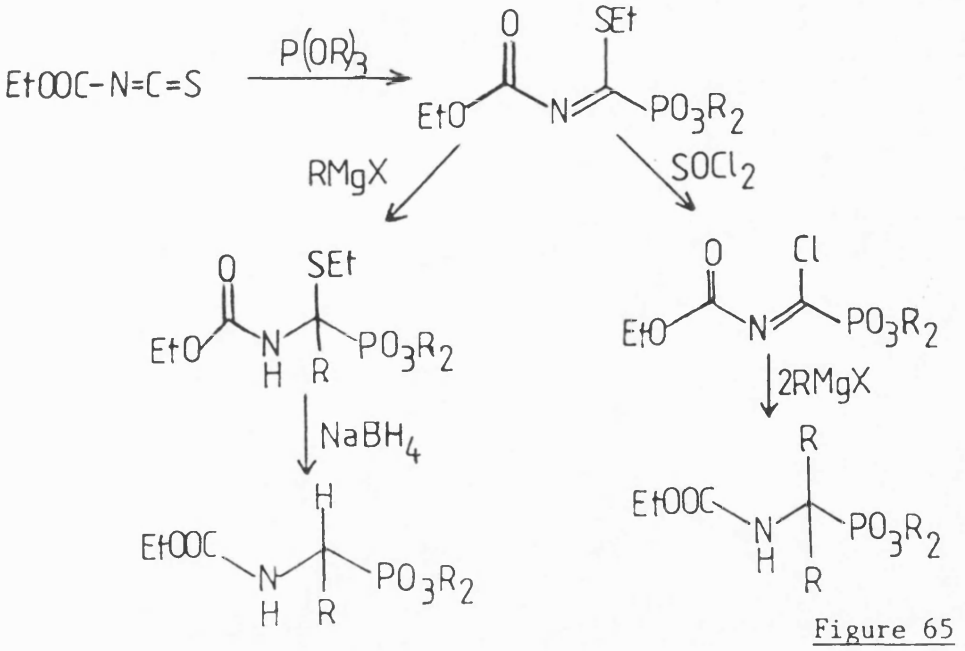
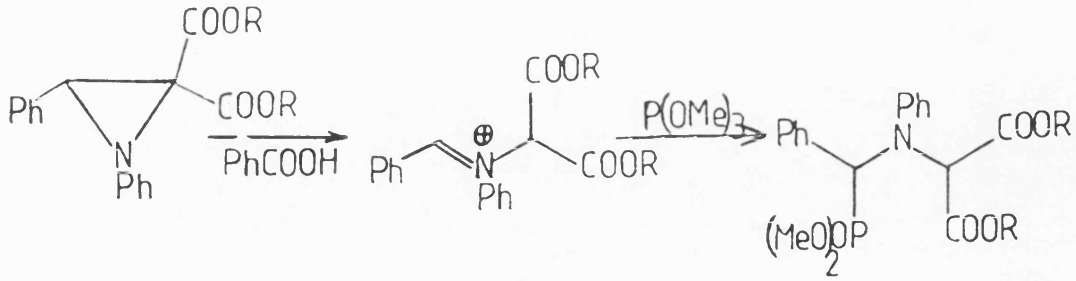


Figure 65

e) with aziridines[93]

i)



ii)

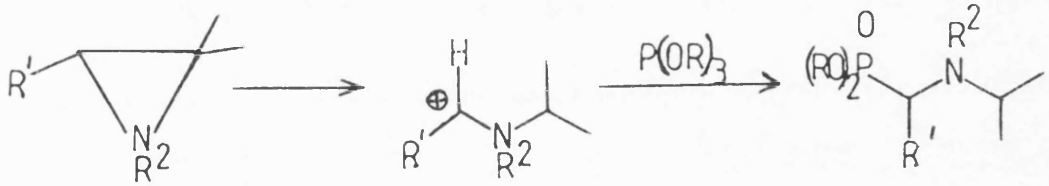
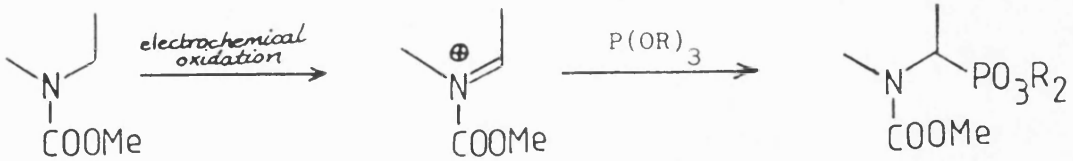


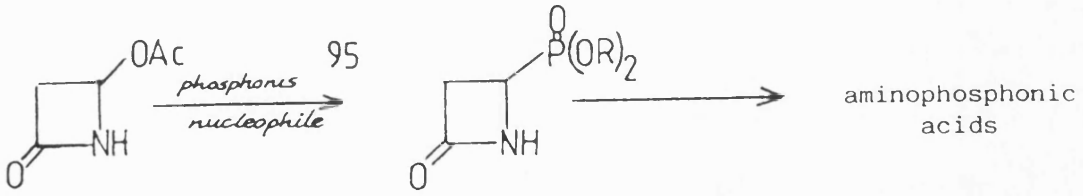
Figure 66

f) with acyliminium ions (and others)[94]

i)



ii)



iii)

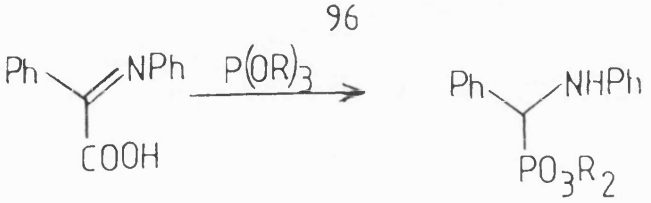


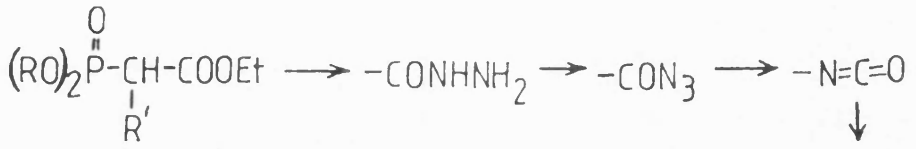
Figure 67

iii) By Rearrangement Processes

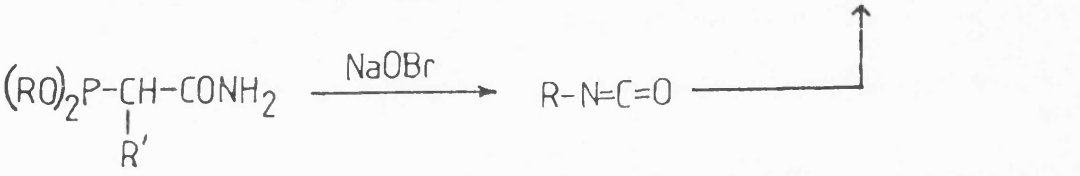
The phosphonate is assembled generally by Arbusov or Michaelis-Becker methodology, but the α-amino functionality is assembled from

a carbonyl function using classical rearrangement processes:-

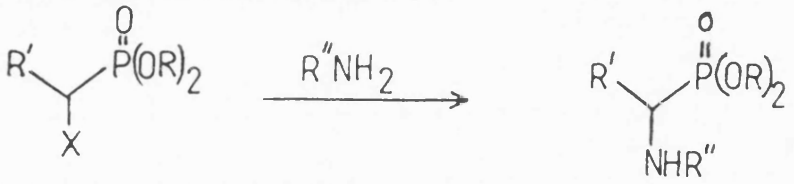
e.g. Curtius-type[97]



Hofmann-type[98]



iv) Displacements α-to Phosphonates:-[99]

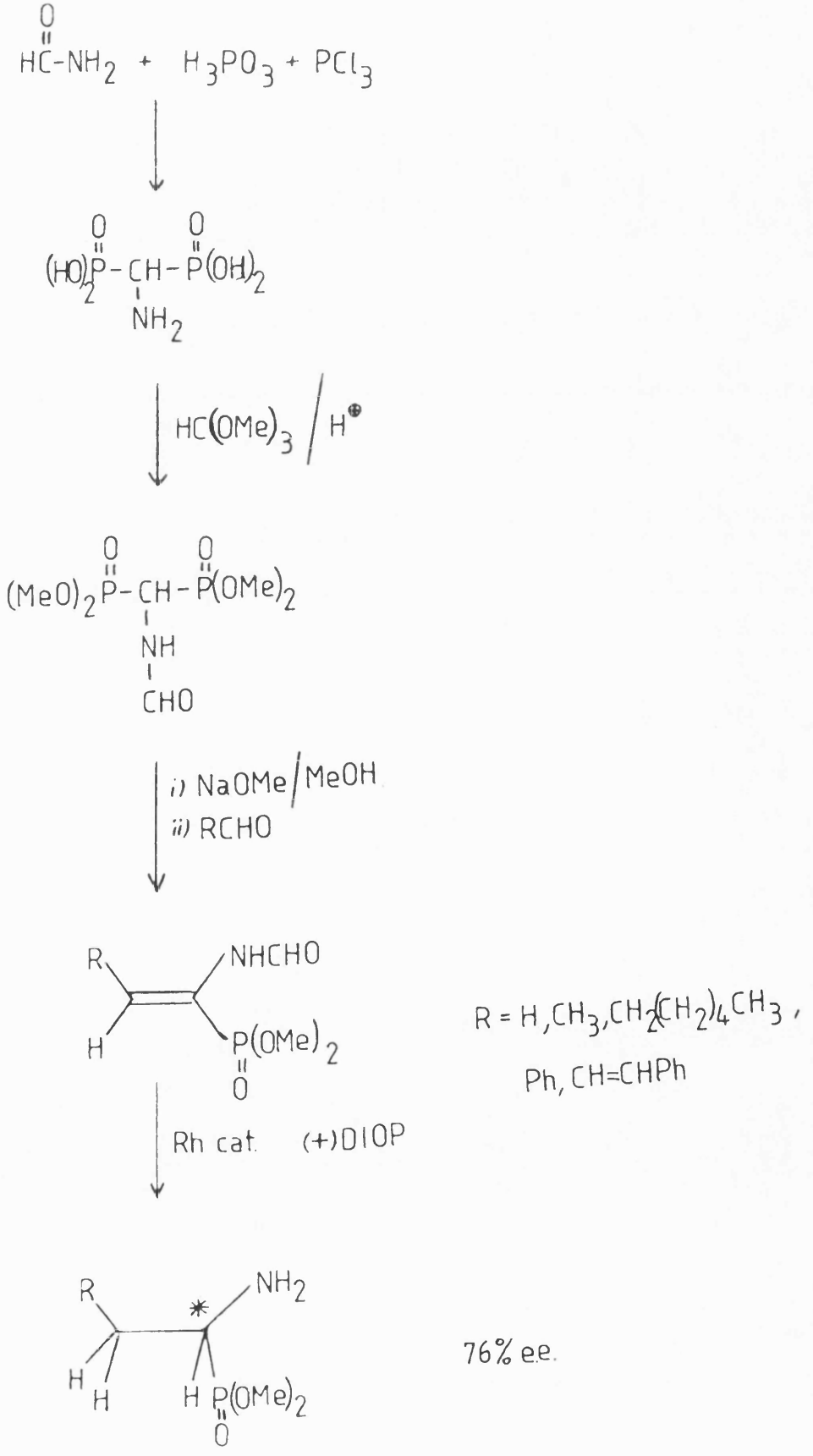


[X = halide, -OH/DEAD/PPh_3]

Figure 68

A chiral approach to α-aminophosphonic acids reliant on an asymmetric hydrogenation has been developed by Schollkopf's[100] group; here the phosphorus is incorporated in a classical fashion (see Figure 69).

Figure 69 - Schollkopf's Approach



A second asymmetric approach developed recently by the Gottingen group[101] employs camphor as a chiral auxiliary to direct alkylation of phosphonoglycine, with high enantioselectivity (see Figure 70).

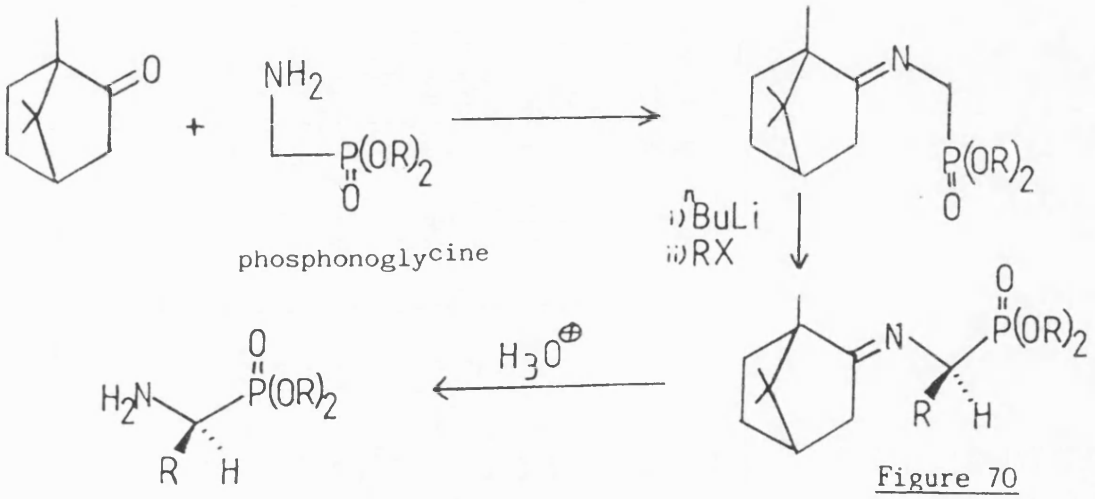


Figure 70

A rather devious approach to the synthesis of optically-active 2-phosphono-azetidinone derivatives, noted by Campbell *et al.*[95] as potential precursors of 1-aminoalkyl phosphonic acid derivatives, has been recently published.[102] Here the α-chirality is controlled in the azetidinone ring closure onto a chiral epoxide (generated from a simple synthon) (see Figure 71).

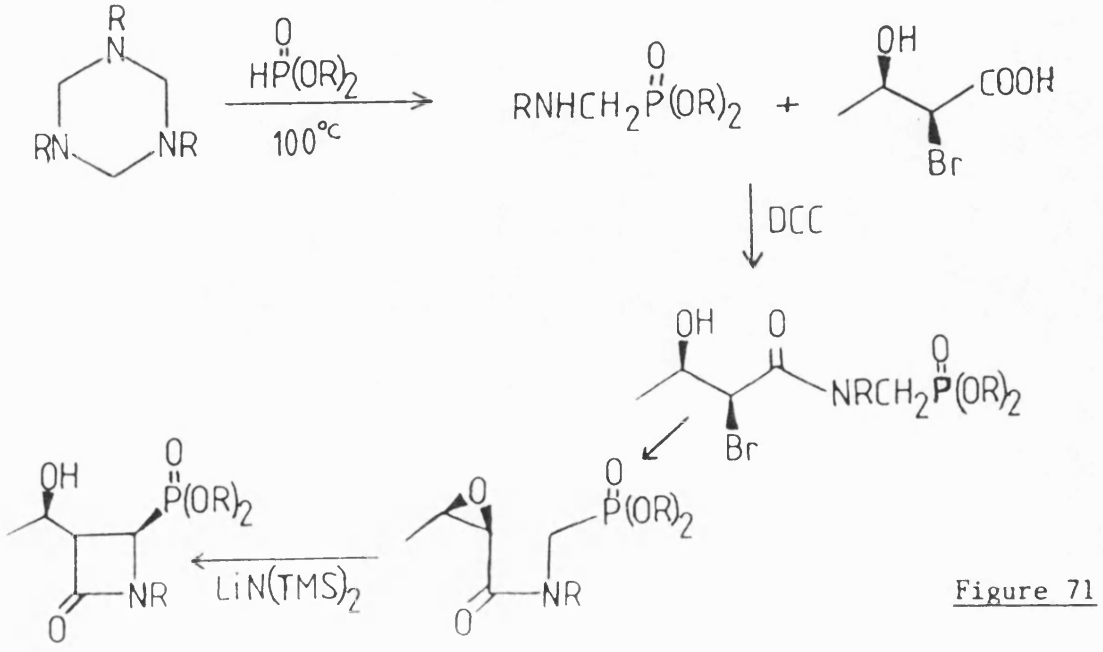


Figure 71

NATURALLY-OCCURRING PHOSPHONATES

Inhibition of Cell Wall Biosynthesis

Aminoethylphosphonates:-

The first natural phosphonate to be isolated (initially from marine protozoa, now known to be more ubiquitous) was 2-aminoethylphosphonic acid[103] (see Figure 72).

Figure 72

Naturally, the biosynthesis of such phosphonates has aroused some interest (see Appendix One for a discussion of biosynthetic mechanism).

A synthesis has been reported,[104] as well as chiral approaches to analogues,[105] *via* aziridines derived from amino acids.

The synthetic dipeptide *Alaphosphin*[106] (L-alanyl-L-1-aminoethylphosphonic acid) was designed as a D-ala-D-ala mimic, seeking inhibitory action in cell-wall biosynthesis.

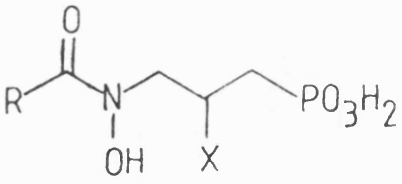
The mode of action is thought to involve three stages:-

i) transport through the bacterial cell-wall by peptide permeases,

ii) intracellular peptidase cleavage,

iii) action of the L-1-aminoethylphosphonic acid on alanine racemase.

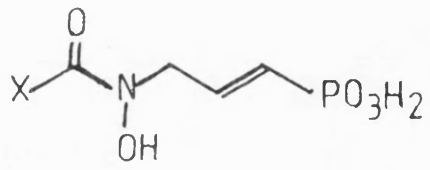
Other phosphonates isolated by workers at *Fujisawa Laboratories*[107] from strains of *Streptomyces* and found to inhibit cell wall growth (Gram positive and Gram negative activity) were of the type shown below (see Figure 73).



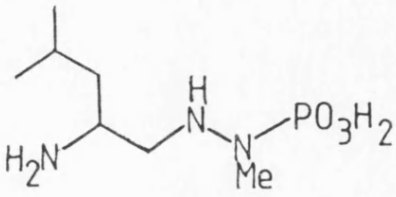
A R=Me, X=H

B R=H, X=H

C R=Me, X=-OH



D

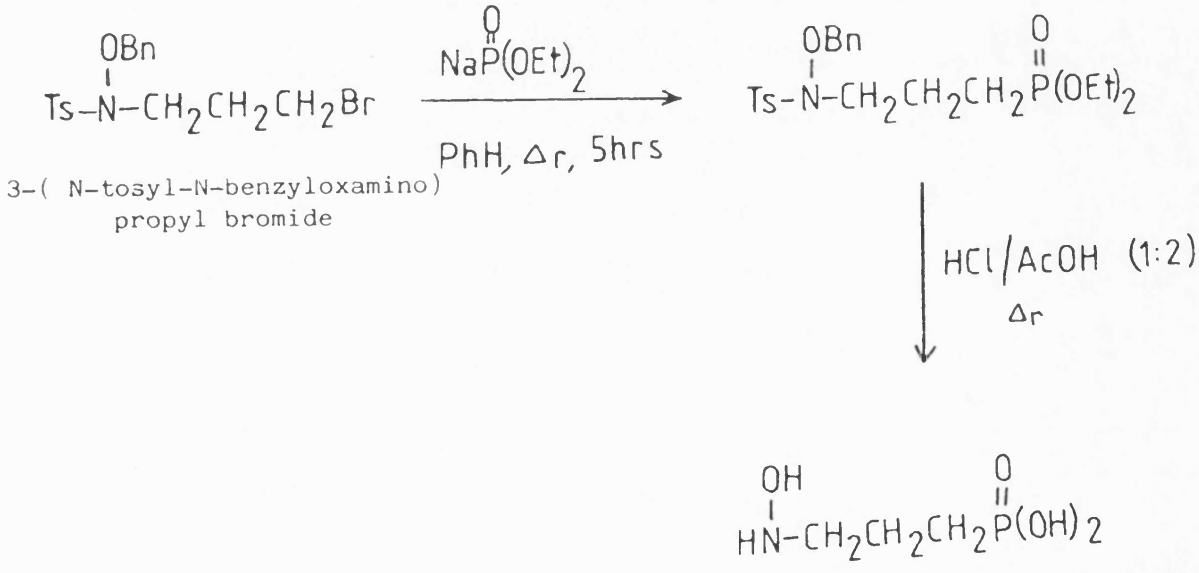


E

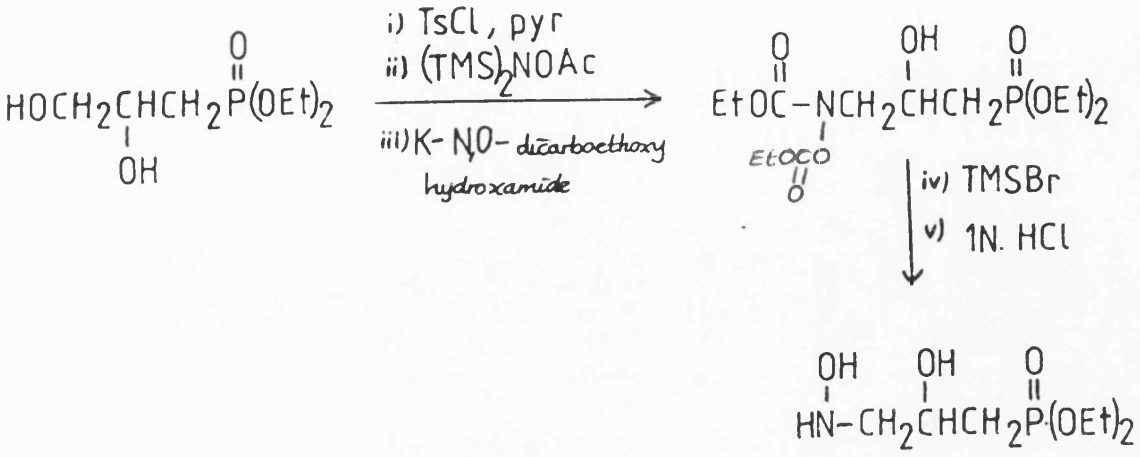
Figure 73

Syntheses of A-D above have been reported[108] (see Figure 74).

A,B



C



D

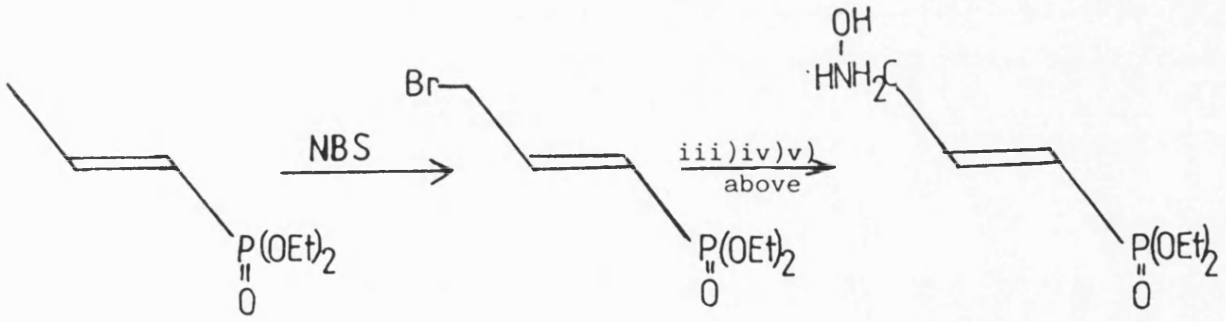
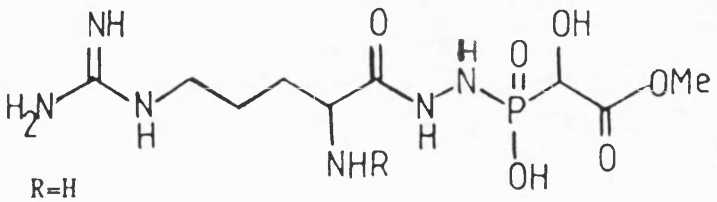


Figure 74

Similarly, the phosphazacins A and B[109] have unique structures (see Figure 75) and activities, though bear passing resemblance to E (above) from Fujisawa.



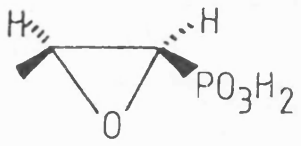
A R=H

B R=COCH(NH_2)^{i}Pr

Figure 75

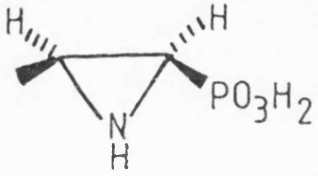
Also active against bacterial cell-wall biosynthesis, by irreversible inhibition of pyruvate uridine diphospho-*N*-acetyl glucosamine,* is phosphonomycin[110] [(-)(*1R*,*2S*)-1,2-epoxypropylphosphonic acid] (see Figure 76), isolated from *Streptomyces fradia*, and the analogous aziridine (shown below, Figure 76.2).

Figure 76



PHOSPHONOMYCIN

Figure 76.2



Phosphonomycin has been synthesised achirally[111] and resolved *via* the quinine salt, thus proving structure and absolute configuration (see Figure 77).

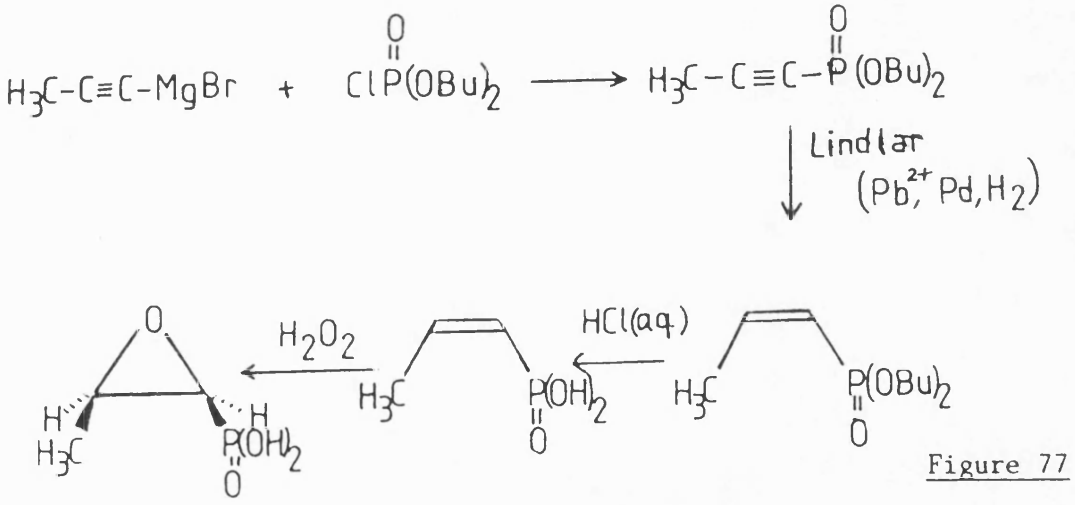
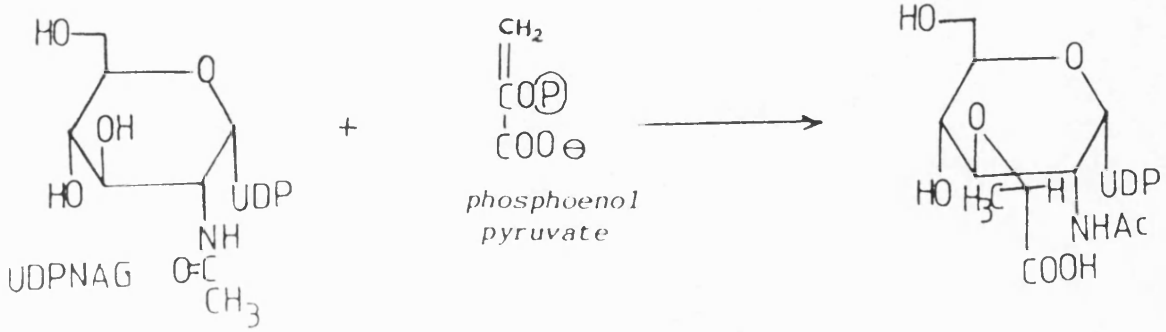


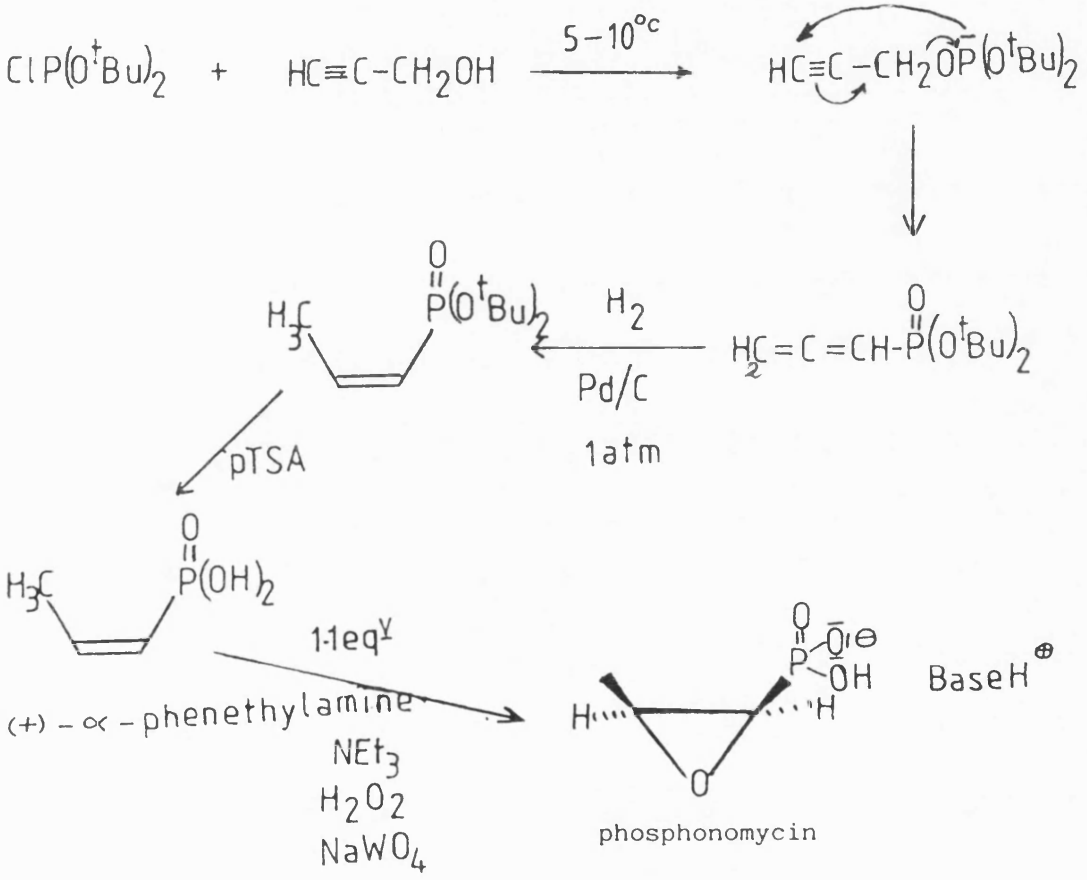
Figure 77

*Footnote:-

The biosynthesis of the peptidoglycan for the cell-wall starts with the formation of activated sugars. Uridine diphosphate-N-acetyl glucosamine and phosphoenol pyruvate combine to form a muraminic acid.



A second synthesis,[112] simpler, more elegant and higher yielding, followed, also from the Merck laboratories. This involved thermal rearrangement to an allenic phosphonate and an expeditious one-step epoxidation and resolution following reduction (see Figure 78).



(-)isomer - crystallises (92% optically pure)

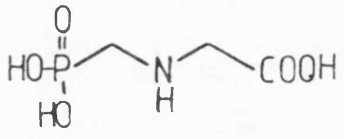
(+)isomer - remains in solution

Figure 78

Inhibition of Amino Acid Biosynthesis

Disruption of amino acid biosynthesis in plants is purported to be an extremely effective method of herbicide action[113 a,b,c] and rationalisation of enzyme inhibition in terms of organophosphonate molecules has been applied in this field.

Glyphosphate, (N-(phosphonomethyl)glycine), for instance is a unique post-emergent herbicide acting by inhibition of aromatic amino-acid biosynthesis (see Figure 79).



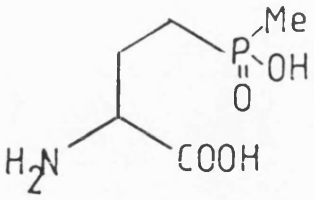
Glyphosphate

Figure 79

A family of biologically-active tripeptides with a terminal phosphonic (or phosphinic) acid have been uncovered which, like alaphosphin, rely on transport through the bacterial cell-wall by peptide permeases, intracellular peptide hydrolysis and action of the released phosphorus-acid on an intracellular enzyme involved in critical amino acid biosynthesis.

The antibiotic phosphinothricin, phosphinothricyl-alanyl-alanine was isolated from *streptomyces hygroscopicus*[114] and *streptomyces uridochromogenes*.[115] A related tripeptide, phosphinothricyl-alanyl-leucine has been isolated from *kitasatosporia phosalacinea*.[116] These are highly active agents agains both Gram-positive and Gram-negative bacteria, entering *via* the oligopeptide transport system.

The 'warhead' of the tripeptide, the novel 2-amino-4-methyl phosphonobutanoic acid (see Figure 80) is itself a herbicide, with activity reputedly based on inhibition of glutamine synthetase.[117]



2-amino-4-methylphosphonobutanoic acid

Figure 80

Glutamine synthetase catalyses the conversion of glutamic acid to glutamine (see Figure 81).

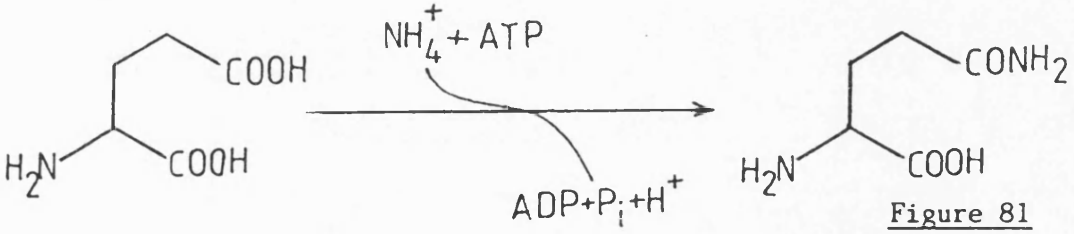
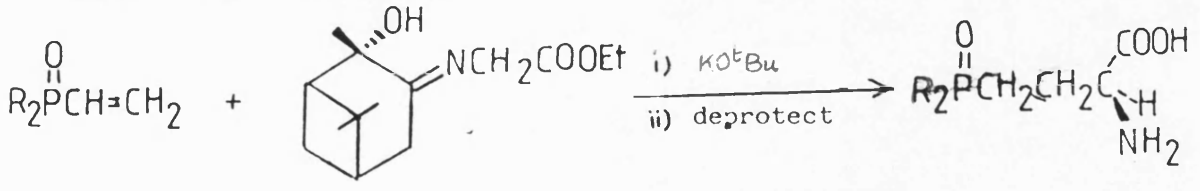


Figure 81

This supposed inhibitory action can be rationalised since the phosphinic acid is an isosteric antimetabolite of glutamic acid.

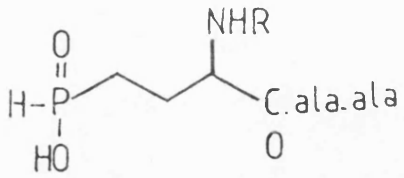
This phosphinate has recently been synthesised in chiral form utilising the bis-lactim ether methodology developed by Schollkopf,[118] and by Minowa,[119] who made use of the Michael addition of a chirally-modified glycine Schiff base to the appropriate vinyl phosphorus compound. [2-amino-4-phosphonobutyric acid was also synthesised.] (See Figure 82.) Only low optical purity was achieved.

Figure 82 - Minowa's synthesis



Other, racemic, syntheses have been reported.[120]

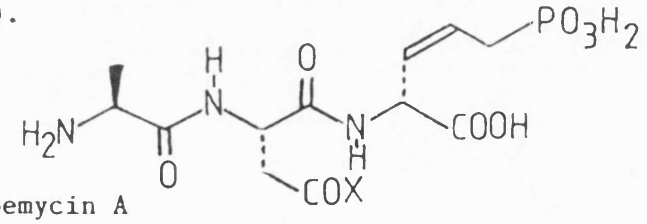
The isolation of the related *bialaphos*[121] which is structurally related to phosphinothricin has been described (see Figure 83).



BIALAPHOS

Figure 83

Also related, in that they are tripeptides containing one novel aminophosphonic acid are the plumbemycins.[122] Plumbemycins A and B were isolated from *streptomyces plumbeus* and assigned as L-alanyl-L-aspartyl-D-2-amino-5-phosphono-3-*cis*-pentenoic acid and L-alanyl-L-asparaginyl-D-2-amino-5-phosphono-3-*cis*-pentenoic acid respectively (see Figure 84).



X = -OH Plumbemycin A

= -NH2 Plumbemycin B

Figure 84

The structure and stereochemistry of the constituent aminophosphonic acid (APPA) have been elucidated and presented as shown below (see Figure 85).

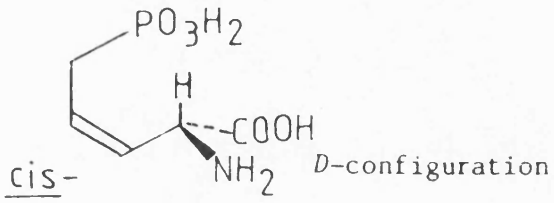


Figure 85

Rigorous analysis of the published data indicates that whilst the *cis*- nature of the double-bond is probably correct (from considera-

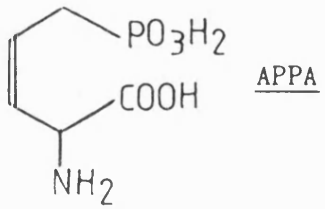
tion of the particular coupling constants), the D-configuration need not be correct.

The absolute configuration was assigned on the basis of the effect of acidification upon optical rotation, a well-known technique which is of debatable value in a structure of this type.

The structure and stereochemistry of the plumbemycins therefore remain to be validated by unambiguous synthesis.

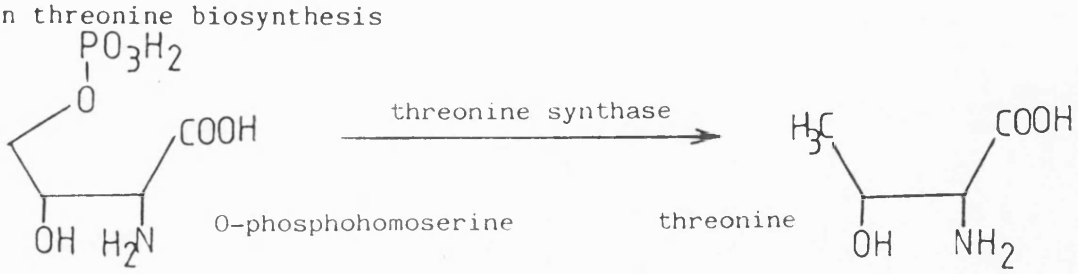
The biological activity of the plumbemycins again relies upon the oligopeptide transport system to carry the 'warhead' phosphonate into the cell; intracellular peptide hydrolysis frees the aminophosphonic acid which has been shown by feeding studies to be an inhibitor of threonine, and to a lesser extent, lysine biosynthesis. Again, this inhibitory action can be rationalised at the level of an individual enzyme in the biosynthetic pathways (see Figure 86).

Figure 86 - Plumbemycin APPA as an isosteric antimetabolite



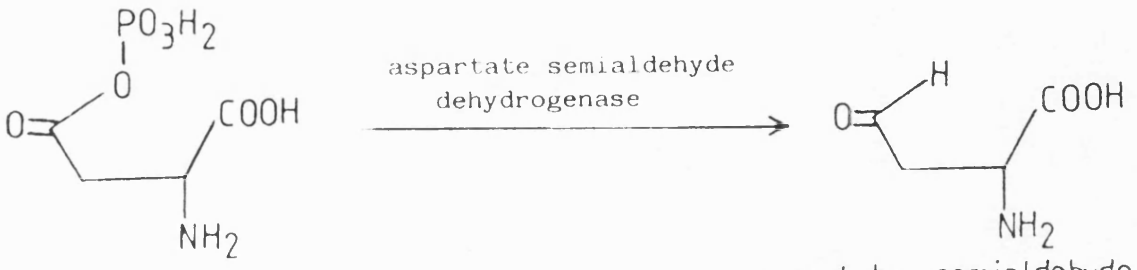
APPA

i) in threonine biosynthesis



O-phosphohomoserine threonine

ii) in lysine biosynthesis



3-aspartylphosphate aspartate semialdehyde

Both of these amino-acids are essential to higher life-forms (i.e. cannot be biosynthesised); therefore inhibitors of enzymes late in the anabolism of such biochemicals ought not to have any obvious detrimental effect on higher species.

DISCUSSION:- Towards the APPA constituent of the Plumbemycins.

Introduction:-

It was the aim of this research to devise a synthesis of the novel aminophosphonic acid constituent of the Plumbemycins. This synthesis would seek to confirm the structural assignment made by Park and his co-workers;[122] particularly the route should serve to determine unambiguously the absolute configuration of the natural material by correlation, *via* synthesis, to material of known chirality.

The Structure of the Plumbemycins:-[122]

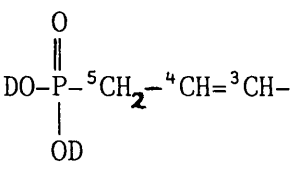
Park reported the isolation of two related tripeptide antibiotics from *Streptomyces plumbeus* and, by utilising standard hydrolytic techniques, he assigned their gross structures as L-alanyl-L-aspartyl-aminophosphonic acid and L-alanyl-L-asparaginyl-aminophosphonic acid, where the aminophosphonic acid was the same in each case and of novel structure.

The topological structure of this aminophosphonic acid was elucidated by analysis of the proton nmr spectrum, whilst the absolute configuration was determined by correlation of the effect of acidification upon optical rotation. These assignments are, perhaps, not conclusive evidence for the structure stated by Park and merit re-examination and validation by synthesis.

The ^1H nmr spectrum (100MHz) of the aminophosphonic acid (in D_2O) shows the following signals:-

δ(ppm)	multiplicity	J(Hz)	integral
6·12	multiplet	-	1H
5·64	d of t	5·2, 9·5	1H
4·81	d	9·5	1H
2·72	d of d	8·4, 23	2H

Park assigned the signals as follows:-



	6·12 ppm	C_4H
	5·64 ppm	C_3H
	4·81 ppm	C_2H
Figure 87	2·72 ppm	C_5H's

The signal at 2·72 ppm (2H, d of d, 8Hz , 23 Hz) was assigned to the C_5 methylene unit, the doublet of doublets arising from coupling to the olefinic proton on C_4 (J=8·4 Hz) and to phosphorus (J=23 Hz). When the signal at 6·12 ppm was irradiated, the doublet of doublets collapsed to a phosphorus-coupled doublet. Thus, the signal at 6·12 ppm may be assigned as C_4H. This assignment was further confirmed by the disappearance of this signal after catalytic hydrogenation of the aminophosphonic acid.

Also disappearing on catalytic hydrogenation was the signal at 5·64 ppm (1H, d of t, J=5·2, 9·5 Hz), suggesting that this was the second olefinic proton, C_3H, having coupling constants of 5·2 Hz due to coupling to phosphorus and 9·5 Hz due to coupling to the protons on C_2 and C_4.

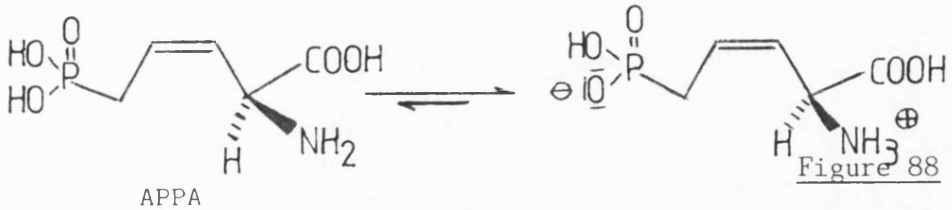
When this olefinic signal at 5·64 ppm was irradiated, the doublet at 4·81 ppm (1H, J=9·5 Hz) collapsed to a singlet; hence this signal was assigned to C_2H. Park makes no comment on the effect of this irradiation on the signal observed for C_4H, and also no irradiation experiment was reported to have been conducted at the resonant frequency of C_2H to directly show the olefinic coupling constant. Park simply assigned the double bond as having a *cis*-configuration on the basis of the 9·5 Hz coupling constant observed indirectly, a *trans*-configuration requiring a larger olefinic coupling constant. A more thorough nmr analysis of the material might have led to greater

confidence in the postulated structure.

Whilst this assignment is probably correct, the method used to determine the configuration of the chiral centre is less secure. It was well known that the absolute configuration of amino acids might be determined by observing the effect of acidification upon optical rotation,but Park's assignment of the material as D-2-amino-5-phosphono-*cis*-pent-3-enoic acid (APPA) on this basis is debatable as the technique may not be applicable to this class of molecule.

The method used, known as the Clough-Lutz-Jirgenson method,[123] depends upon a distortion of the equilibrium between the zwitterionic form and the neutral form of a monoasymmetric α-amino acid undergone on acidification of an aqueous solution. In acid solution, the carboxyl group will remain protonated due to the increased acidity. Obviously, the amine group remains protonated, associating with the conjugate base of the acid. This distortion causes changes in the electronic field of the molecule, which directly influences the observed optical rotation of the molecule.

However, the amino acid in question, APPA, has an intrinsic phosphonic acid group and this itself is a strong acid and so will dissociate in aqueous solution (see Figure 88).



APPA

Figure 88

Thus the chiral α-amino acid centre is already in a situation comparable to the protonated amino acid (in acid solution) and so the effect of acid addition on the optical rotation of the solution may be less pronounced than expected, and a less predictable method for the assignment of absolute configuration.

Thus a synthetic strategy must be decided upon which will allow absolute control over the chirality of the product amino acid. Also, a means of controlling the geometry of the double-bond must be included in the strategy, as well as the obvious questions of introduction of the many functionalities addressed.

Devising the Synthetic Strategy:-

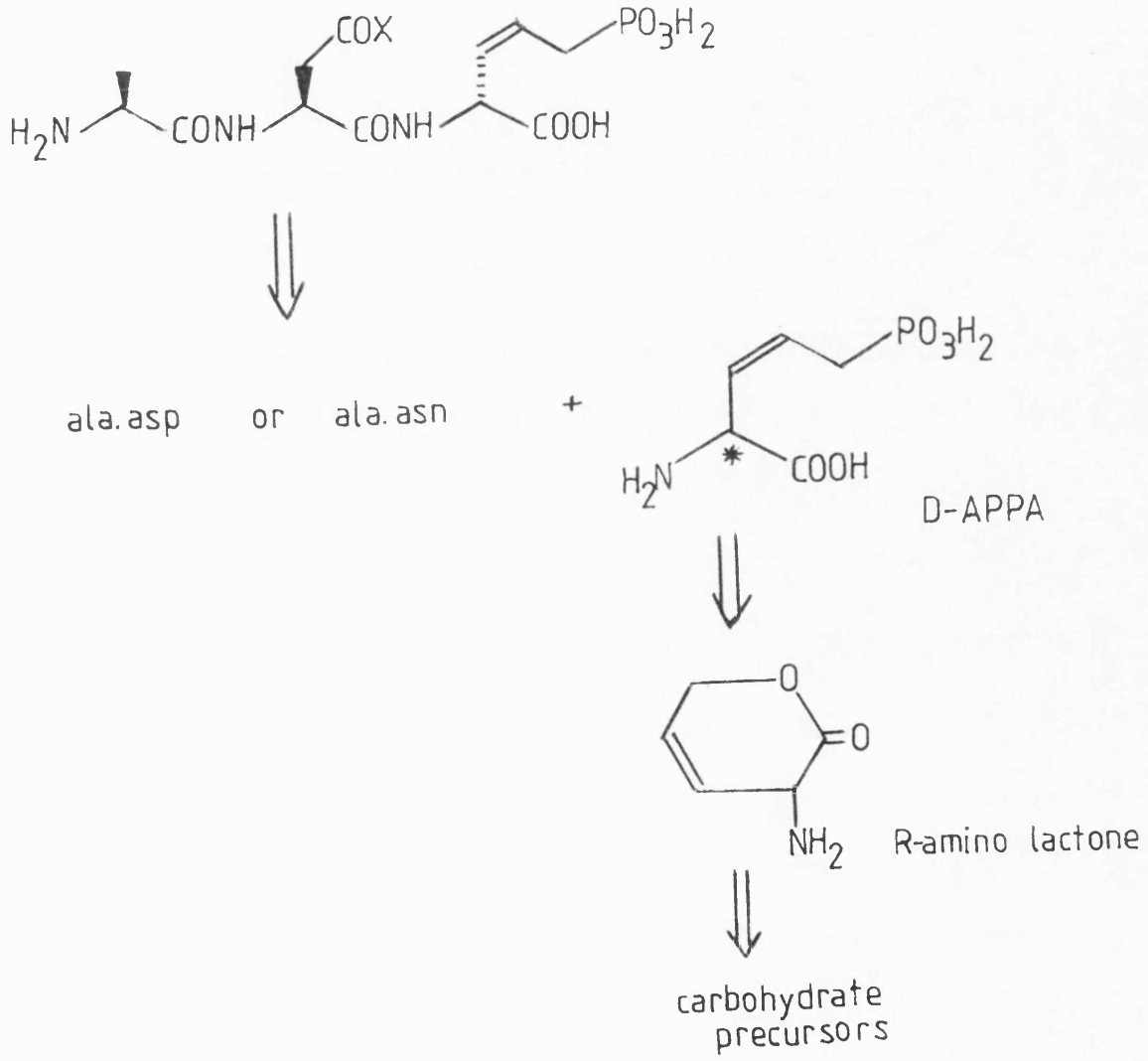
The necessity for absolute stereocontrol in the synthesis suggested that a way be found to our target molecule from a member of the chiral pool,[124] which present pre-existent functionality and chirality, suitable for manipulation in controlled fashions.

The *cis*-geometry of the double bond presents a special challenge as many methods for the introduction of unsaturation tend to give *trans*-products. Also, it should be noticed that the double bond is out of conjugation with both the α-carboxylic acid and the ω-phosphonic acid, whereas introduction of unsaturation by, for instance, an eliminative process would tend to give conjugated material.

However, it is obvious that unsaturation constrained in a small ring is by necessity of *cis*-geometry. Furthermore, the α-amino acid centre is equivalent to an amino lactone unit, approachable from a carbohydrate. Thus, we have the skeleton of a strategy (see Figure 89).

Figure 89

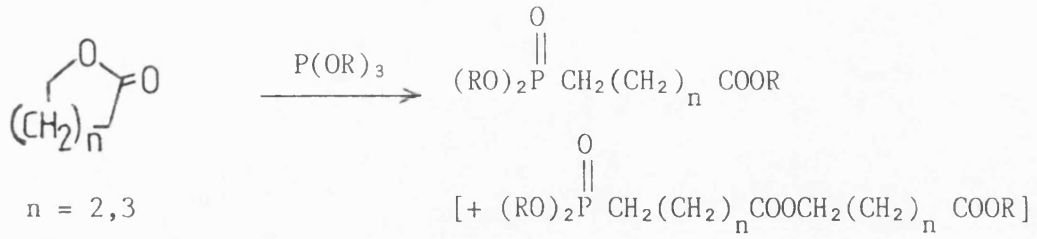
The Plumbemycins - A Retrosynthetic Analysis



The key transformation in the synthetic strategy is the incorporation of a phosphonate moiety, essentially by a lactone *O*-alkyl ring-opening process. There is some precedent for processes of this kind occurring directly[125] (see Figure 90), and also ways may be envisaged of achieving the transformation indirectly.

Figure 90

Direct Incorporation of Phosphorus

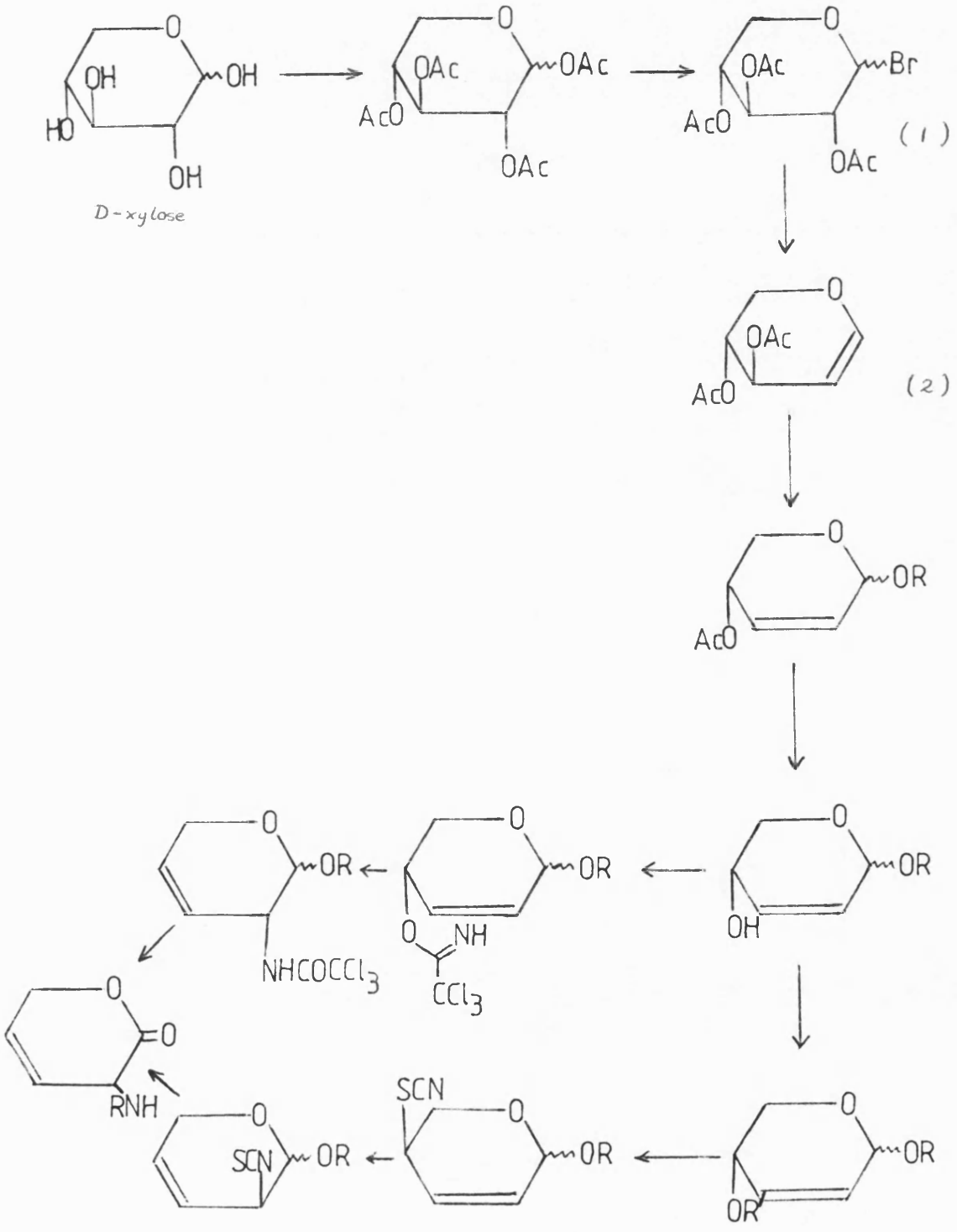


The use of carbohydrate materials as 'fuels' for chiral synthesis has become popular in recent years[124,126] due to their ready commercial availability, cheapness, high degree of functionality and the possibility of utilisation and manipulation of pre-existing chiral centres in fixed-ring systems. A route from a carbohydrate starting material (D-xylose) to amino lactones of the desired structural type is outlined in Figure 91.

Outline of Synthetic Approach to APPA

Figure 91

Rearrangement Chemistry of Unsaturated Sugar Systems



Synthesis by Manipulation of Unsaturated Sugar Systems[127]

The retrosynthetic analysis conducted showed that the target molecule, an amino lactone, might be approached from D-xylose, *via* its unsaturated xylal derivative (2).

Generally, glycals have been produced following the classical method of Fischer and Zach, involving the reduction of poly-*O*-acetyl glycosyl halides with zinc in aqueous acetic acid. Our attempts to prepare 3,4-di-*O*-acetyl xylal have centred on an improvement of the original method, developed by Helferich, Mulcahy and Ziegler,[128] who carried out the acetylation of the free sugar with acetic anhydride in the presence of perchloric acid as a catalyst and, without isolation of the peracetate, treated it with HBr generated in the reaction mixture by the addition of phosphorus tribromide, also generated *in situ*, after the method of Barczai-Martos and Korosy.[129]

The bromide, which could be isolated or used directly, was reduced by treatment with activated zinc dust. This reduction step (which has been postulated[130] as proceeding by the addition of two electrons from the metal to the C-1 carbonium ion, generated by primary ionisation of the glycosyl halides, and the elimination of the C-2 acetoxy anion from the resulting carbanion) has been found to be critically temperature-dependent[131] and it has been pointed out that inadequate control may result in the replacement of bromine by acetoxy- (or hydroxy-), and the formation of side-products.

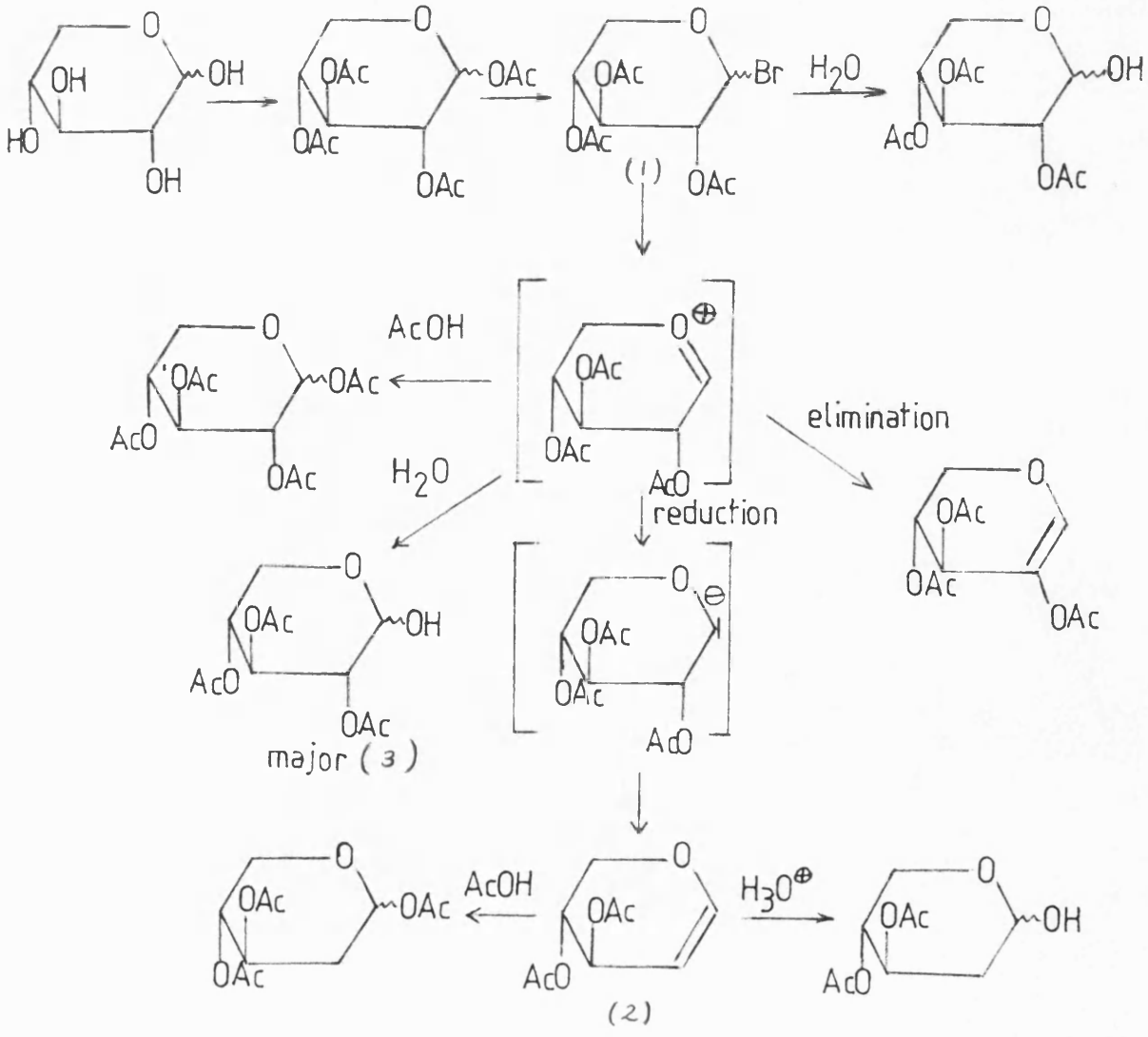
The yield of *O*-acetyl glycals has been found to be dependent on the activity of zinc, so various activation processes[132] were employed to try and improve yields of the desired product (though their value had been challenged).[131] A recent report[133] of the synthesis of furanoid and pyranoid glycals by a reduction with zinc activated by silver on graphite in THF was not repeated here, though

yields were reported as much improved.

Perhaps because of competition from one or more of the number of possible alternative reaction processes (see Figure 92 below) which can be envisaged as occurring, the yield of the known 3,4-di-*O*-acetyl-D-xylal (2) isolated by chromatography was in the region of 20%.

Figure 92

Side Reactions Possible in the Xylal Reaction



Since the major isolated product of the reaction was identified as the alcohol formed by H_2O solvation of the carbonium ion intermediate, attempts were made to eliminate water from the reaction sequence, including a return to the use of HBr-glacial acetic acid for bromination,[128] and the use of various non-aqueous systems (involving CF_3COOH, HOAc/DCM, HOAc/THF) to conduct the zinc reduction. These modifications were unsuccessful in producing the desired xylal product in increased yield (if at all).

Other routes to glycals have appeared in the literature,[134] though none are directly relevant to the provision of *O*-acylated glycals. Attempts to treat *O*-acyl-protected xylopyranosyl bromide (*1*) with Na-naphthalenide, and magnesium in a Grignard-type process, were both singularly unsuccessful.

The 3,4-di-*O*-acetyl xylal (*2*) available was then rearranged to the 2,3-unsaturated pseudo(Ψ)-xylal species (*4*,*5*) by reaction with an alcohol, under Lewis acid catalysis.* Ferrier and his group,[135] in their original studies, utilised BF_3-etherate to catalyse the rearrangement, but an improved method of converting the 3,4-di-*O*-acetyl xylal (*2*) to the methyl 2,3-unsaturated rearranged material (*5*) has been recently reported using $SnCl_4$ catalysis.[136] Presumably, stannic chloride forms a better leaving group than does boron trifluoride.

Ferrier observed that the rearrangement reaction seemed to be dependent on there being a *trans*-relationship between the acetyl

* *Footnote*

This Ferrier reaction might also be useful for the synthesis of more complicated glycosides, as it also occurs with more complex alcohols in benzene solution.

groups on C-3 and C-4 (hence our choice of xylose as our starting material), suggesting that there is a degree of anchimeric assistance in the displacement of the acetyl group. This restriction has since been shown to be irrelevant when performing the reaction with $SnCl_4$ catalysis.[136]

Closer analysis of the postulated mechanism raised the possibility of partial, or indeed complete, racemisation of the products (see Figure 93 below). However, the products possessed optical activity and , as will be described later, were subsequently carried through to optically-pure products.

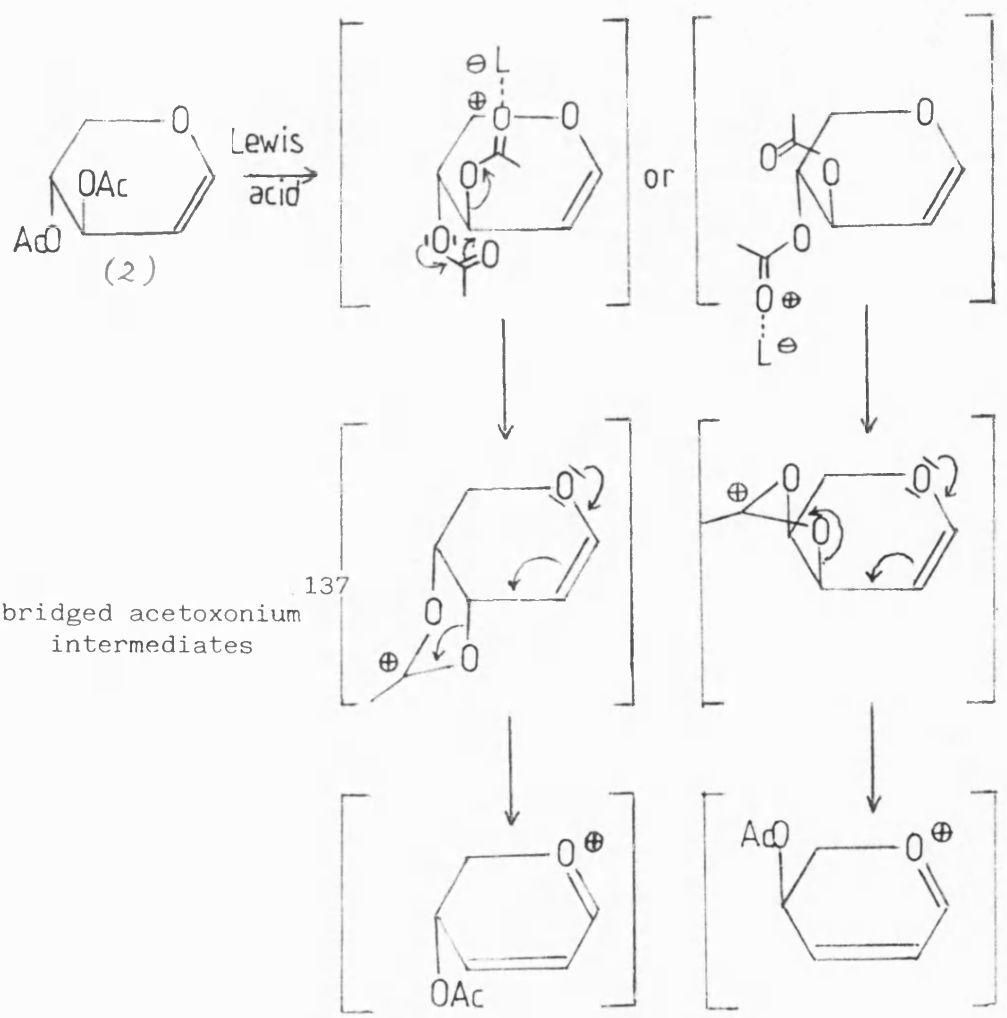


Figure 93

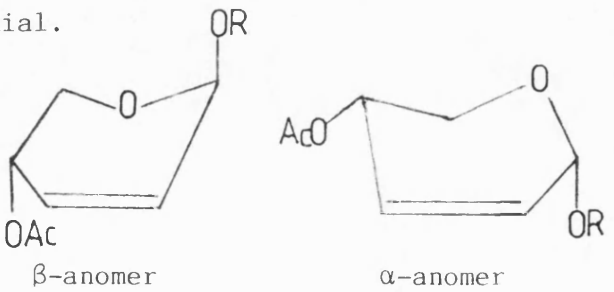
Alcoholysis of the planar carbonium ions gives rise to a mixture of anomers, in unequal quantities (see Figure 94). Re-equilibrium of the anomers on partial separation has been reported[136] (by re-introduction to the conditions of the reaction).

The fact that this racemisation procedure did not seem to occur would appear to indicate that the neighbouring C-4 acetyl group is secondary in effect to the conjugated ring oxygen atom in assisting Lewis acid complexation at the acetyl group on C-3.

[R = Me, Et]
(5) (4)

Figure 94

The structures of these, and their anomeric assignment, could be determined directly, or by correlation with their derived alcohols which had previously been subjected to a detailed ^{1}H nmr analysis by Fraser-Reid and his co-workers.[138] This analysis also suggested that the half-chair conformations (see Figure 95) adopted by these materials were controlled by the anomeric effect, both glycosidic units being axial.



(This conformational control exerted will be remarked upon later.)

Figure 95

The ^{13}C nmr spectra of these two also supports the assignment of the anomeric configurations, since the α-anomeric C_1 signal is characteristically at slightly lower field than the β-anomeric C_1 signal.[139] Here the major isomer's C_1 signal falls at 92·9 ppm whereas the corresponding signal from the minor isomer occurs at 94·2 ppm.

It would also be instructive here to consider the characteristic fragmentations observed in the mass spectra of these 2,3-unsaturated materials (see Figure 96).

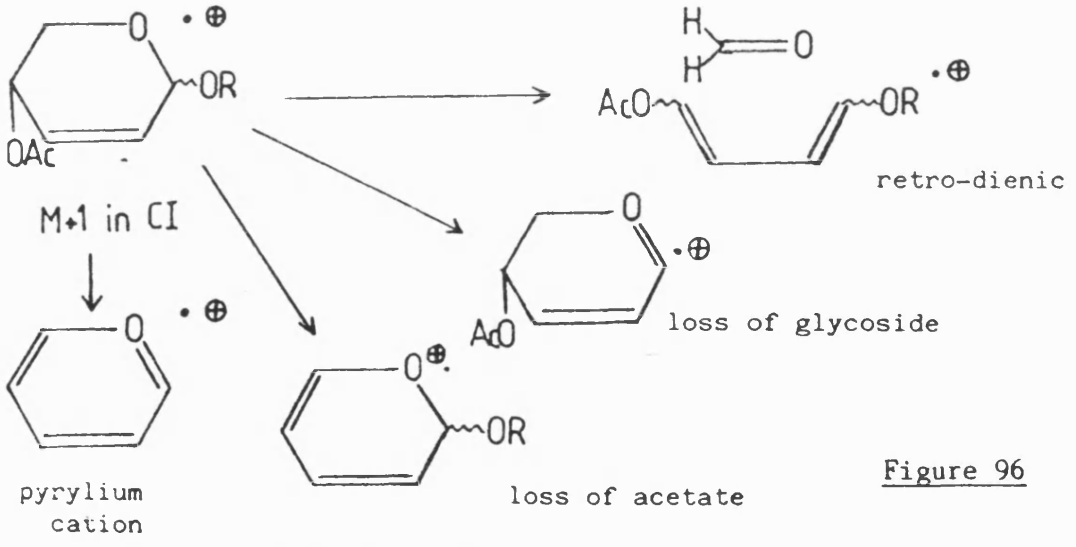


Figure 96

The retro-dienic fragmentation is exceptionally useful, being indicative of the position of unsaturation in the ring.

In our synthetic strategy, however, this production of a mixture of anomers should have broadly proved to be unimportant, both anomers being converted to a useful product by oxidation. This was only partly true; the anomers led to added subtlety when the subsequent rearrangement processes were considered.

Another procedure exists in the literature for the xylal (2) to pseudoxylal (4,5) rearrangement reaction using a palladium-mediated displacement of the allylic acetate.[140] Dunkerton and his

co-workers suggested that the reaction of 3,4-di-*O*-acetyl xylal (**2**) with palladium dichloride in methanol resulted in a 98% yield of one anomer of the 2,3-unsaturated compound (5).

However, when this reaction was repeated, gc-analysis of the reaction mixture indicated a mixture of anomeric products resembling that produced in the BF_3- etherate- or stannic chloride-catalysed reactions.

Interestingly, the addition of a Lewis acid to a solution of the xylal material (2) causes dimerisation[141,145] (see Figure 97).

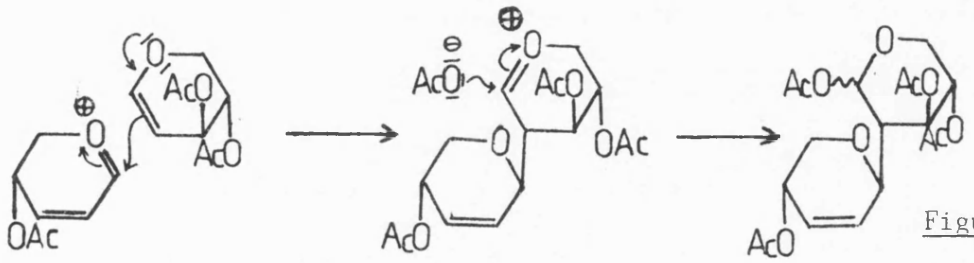


Figure 97

This suggested the possibility of using the Ferrier rearrangement with a variety of other nucleophiles; such processes have been studied, but are complicated by reaction at both C_1 and C_3 (see Figure 98).

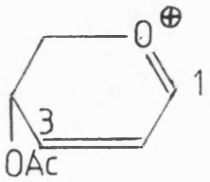


Figure 98

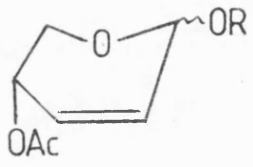
Footnote :

1. *These 2,3-unsaturated sugars have been extensively studied as synthetic intermediates, having been utilised in a great variety of ways.*

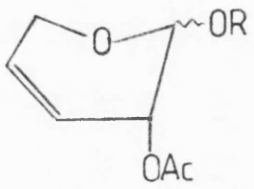
B. Fraser-Reid, Acc. Chem. Res., 1975, 8, 192.

Nucleophiles studied include enol ethers,[142] silyl enol ethers,[143] furan and thiophene,[144] sodium salts of carbon acids[145] and also phosphites.[146]

Originally, one of the reaction products from the Ferrier rearrangement was assigned (wrongly) as the product of a six-electron pericyclic rearrangement, since the olefinic signals in the ^{13}C nmr were markedly different, suggesting one product to be more symmetric than the other (see Figure 99).



asymmetric olefin



symmetric olefin

Figure 99

^{13}C nmr data δ(ppm)

less mobile material (β-anomer)	131·0, 125·0	asymmetric
more mobile material (α-anomer)	129·5, 128·7	symmetric

The structure has now been reassessed, and assigned in agreement with Fraser-Reid's earlier analysis,[138] and the retro-dienic fragmentation in the mass spectrum, as simply one of the anomeric pair. However, it was observed that such a rearrangement process might be adopted for use in the synthesis.

Such [3,3] sigmatropic rearrangements in cyclic allylic systems involve suprafacial migration, so asymmetry at the initial allylic centre is self-immolatively transmitted to the new centre.

Indeed, Overman's rearrangement process,[147] wherein an allylic alcohol is transposed to a rearranged allylic amide, *via* a trichloroacetimidate derivative, is perfect for the required transformation (see Figure 100).

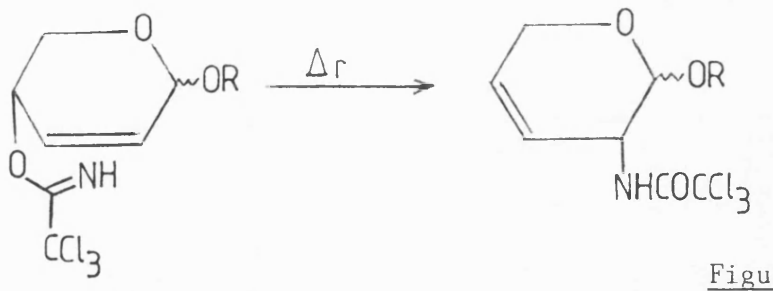


Figure 100

(8) (9)

The large driving force resulting from the increased stability of the amide product over the imidate starting material (~14 kcal mol^{-1}) makes the rearrangement essentially irreversible.

First, it was necessary to deprotect the allylic acetates to the allylic alcohols for further derivatisation. A simple trans-esterification in methanol, catalysed by K_2CO_3, sufficed. These materials were identical with those previously characterised by Fraser-Reid[138] (see Figure 101).

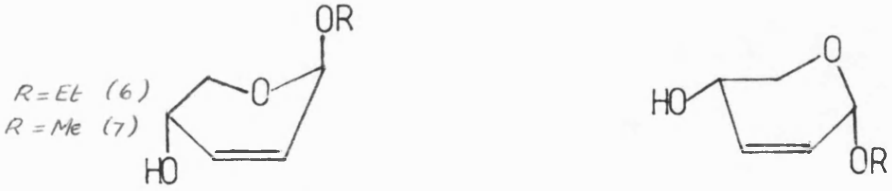
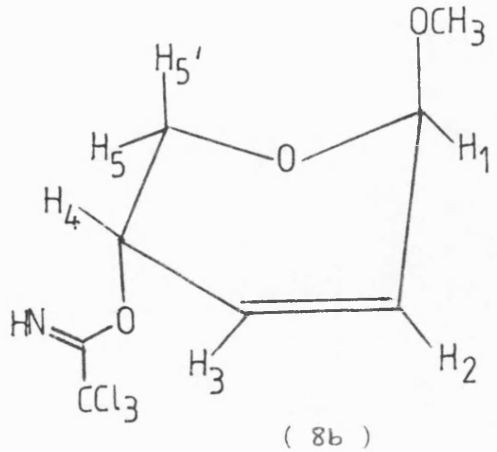


Figure 101

Separation of the anomers could be effected at either the acetate or the alcohol level, though it was simpler to separate the alcohols (50% EtOAc in petroleum ether). [It should be borne in mind that the α-anomeric allylic alcohol is moderately unstable.][148]

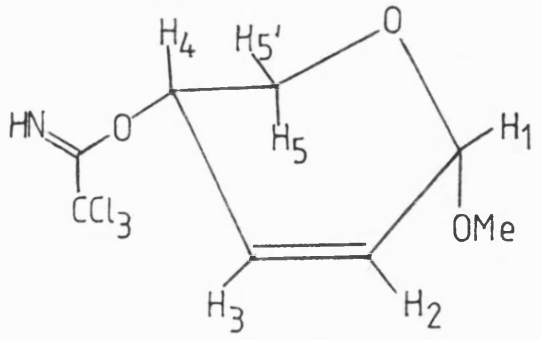
The allylic alcohols were readily derivatised as trichloro-acetimidates (8) by treatment with trichloroacetonitrile (and catalytic sodium hydride),[149] without competitive elimination. The ^1H nmr spectra were sufficiently similar to those obtained for the allylic acetates (4,5) and alcohols (6,7) to suggest that the two anomers adopt similar ring conformations (see Figures 102, 103).



(8b)

β-anomer	(90% Yield)
H_1	4·94 ppm
H_2	6·1 ppm
H_3	6·2 ppm
H_4	5·1 ppm
$H_{5'}$	4·2 ppm
H_5	4·0 ppm
N=H	8·25 ppm
-OMe	3·38 ppm

Figure 102



(8a)

α-anomer	(96% Yield)
H_1	4·7 ppm
H_2	5·7 ppm
H_3	5·9 ppm
H_4	5·3 ppm
$H_{5,5'}$	3·85 ppm (coincident)
N=H	8·1 ppm
-OMe	3·37 ppm

This material shows far more complex coupling

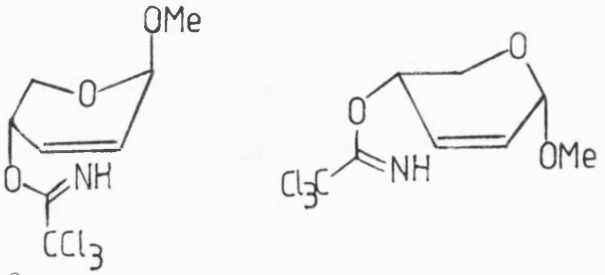
Figure 103

The signal for the anomeric proton in the β-anomer (8b) above was a doublet ($J_{1,2}$ = 3·0 Hz) completely lacking any long-range coupling. This indicates (after Fraser-Reid)[138] that a pseudoequatorial orientation is required for C_1H. Similarly no long-range coupling was observed from H_2 to H_4, so consideration of possible

4-bond allylic couplings[150] suggest that C_4H must also be in a pseudo-equatorial orientation. The couplings observable to the C_5 methylenic unit also implies the adoption of a half-chair conformation (see Figure 102).

The α-anomer (8a) is more complicated to assign, but simple comparison to the spectrum of the previously-assigned alcohol (7a) allowed us to conclude adoption of the conformation shown above (see Figure 103).

These imidates (8) (ν_{max} C-N=H 1660 cm^{-1}; retro-dienic fragmentation characteristic of 2,3-unsaturation) were then rearranged thermally to the allylically transposed amides (9) (ν_{max} C=O 1710 cm^{-1}; retro-dienic fragmentation characteristic for 3,4-unsaturation) in refluxing xylene.[149] It was now that differences in the reactivities of the two anomers began to be observed (see Figure 104).

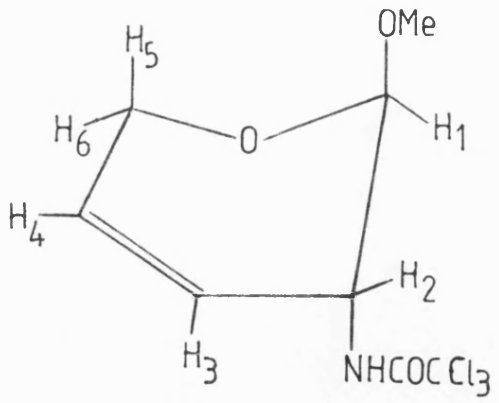


β-anomer — MAJOR — (8b)

α-anomer — MINOR — (8a)

Figure 104

The β-anomer (8b) was quite readily rearranged to give the desired amide product (>80%) (Figure 105).



NH	6·69 ppm*
H_1	4·71 ppm
H_2	4·27 ppm
olefinic	5·82 ppm
olefinic	6·08 ppm
H_5	4·23 ppm
H_6	4·12 ppm

(9b)

*(slowly exchangeable)

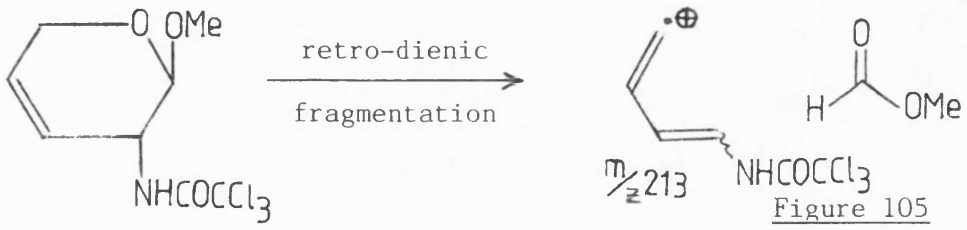


Figure 105

The α-anomer (9a) however underwent much slower reaction (several days) and became considerably charred by prolonged exposure to the reaction conditions. This difference in reactivity may be explained by considering the transition state necessary to allow reaction and the consequent strains inherent in each anomer achieving this transition state; particularly, the stabilisation of reaction conformations conferred (in xylene) by the anomeric effect must be considered (see Figure 106).

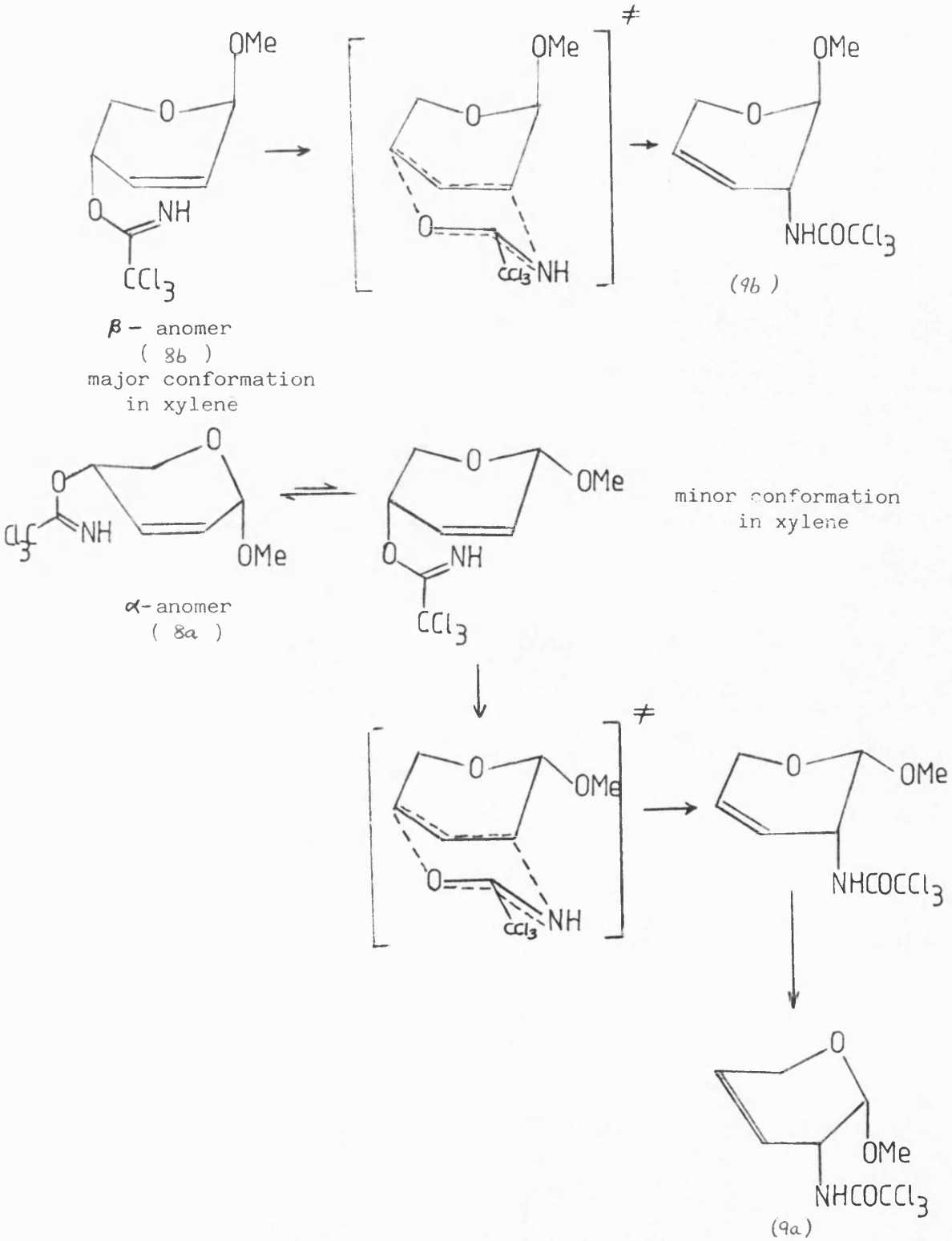


Figure 106

Footnote:

It should be noted that this rearrangement may be conducted on the mixture of anomers, though this is a compromise, removing the necessity for separation of the anomers, and care must be taken not to allow too long for the reaction, or loss due to charring becomes substantial.

Thus a rearrangement process had been found which worked well for one anomer (*86*) (where the arrangement of pendant groups is *ANTI*) but much less well for the other anomer (*8a*) (where there is a *SYN* arrangement of groups). It would be satisfying either if this rearrangement process could be made to function well with both anomers or if a complementary process could be applied which reversed the ease of anomeric rearrangement.

Overman originally reported a dramatic catalysis of this rearrangement process by the addition or mercuric trifluoroacetate,[147] but this was only effective where the imidate was derived from a primary allylic alcohol. Secondary- and tertiary-imidates were reported to suffer from a competing elimination reaction, considerable trichloroacetamide being isolated. Overman also observed formation of α-adducts, rather than rearranged β-amide products, particularly with imidates derived from cyclohexenols.

Treatment of the imidates with Lewis acids (or protic acids) result, in general, in loss of stereochemical and regiochemical control or simple failure of the reaction, with disappearance of the imidate without formation of any amide (see Figure 107).

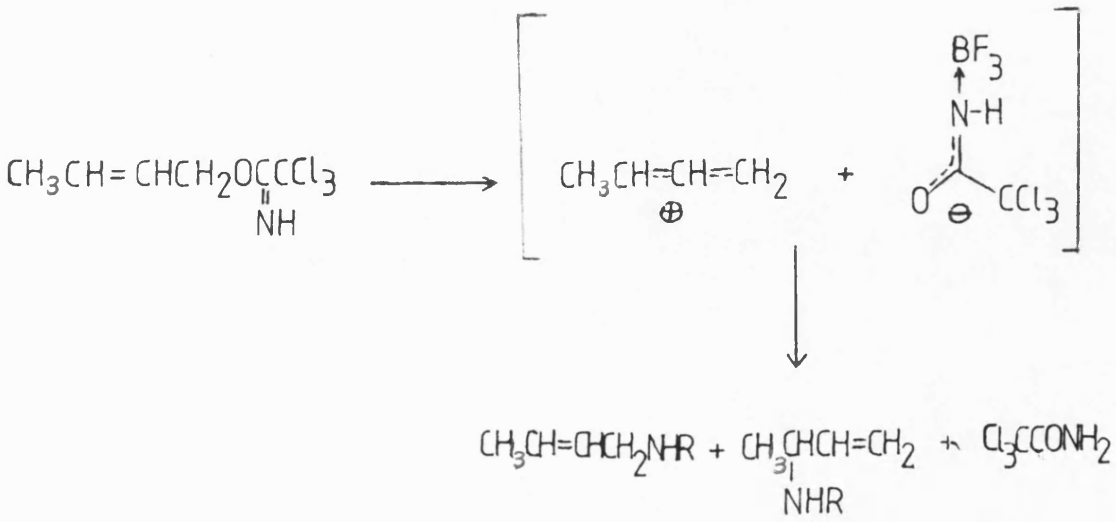
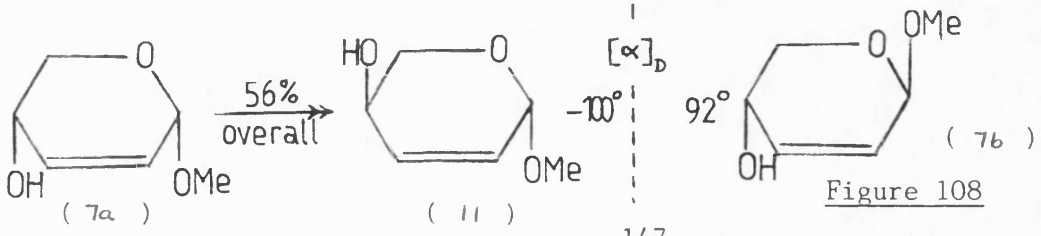


Figure 107

Recent reports of catalysis of such processes using transition metal complexes[151] [namely $PdCl_2(PhCN)_2$ or $PdCl_2(MeCN)_2$] were interesting, proceeding with high (though not complete) stereocontrol. Attempts to use these catalysts here were unsuccessful.*

Development of complementary rearrangement methodology was first simply achieved by an inversion of the allylic alcohol (using the Mitsunobu methodology;[152] DEAD,PPh_3 and an acid (benzoic), followed by deprotection). This DEAD-mediated esterification proceeds in a regio- and stereospecific manner with inversion, without trace of competitive S_N2' displacement or dehydration, at once turning the previously *syn* α-anomer (7a) to the more readily rearranged *anti* alcohol (*11*) (after deprotection), whose enantiomer (7b) had been previously characterised. Their ^1H nmr spectra were superimposable, and the optical rotation reversed (see Figure 108).



(7a) (11) (7b)

Figure 108

Thus application of the Overman rearrangement[147] to the inverted alcohol (*11*) produces similarly inverted amide material (*13*), allowing entry to either enantiomeric series readily from one chiral starting material (see Figure 109) .

Footnote:

Interestingly, Dunkerton[140] reported a sodium cyanoborohydride-promoted allylic rearrangement of several C-6 substituted pyranoside glycals.

However, both $NaBH_3CN$ and a coordinating group at C-6 are necessary to effect the regioselective rearrangement, so pentose glycals do not react in this fashion.

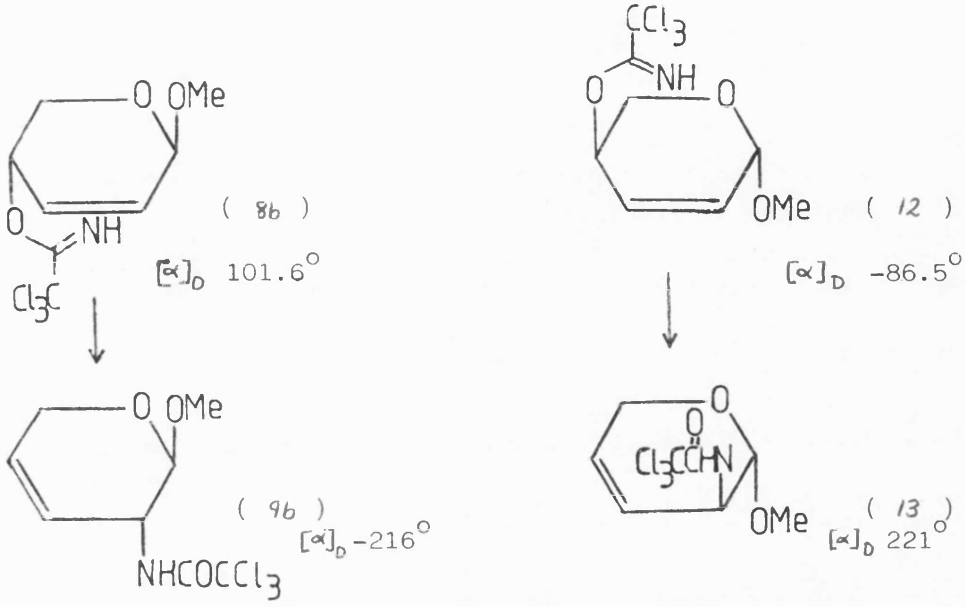


Figure 109

The Overman rearrangement proceeds with suprafacial control, but the other enantiomeric series can be approached (as shown above) by including an inversion process in the synthesis, giving overall antarafacial rearrangement.

A second rearrangement process[153] for the 1,3-transposition of an alcohol to an amide (though less directly) which occurs with an intrinsic inversion involves the rearrangement of a thiocyanate to the complementary thermodynamically more stable allylic isothiocyanates (see Figure 110).

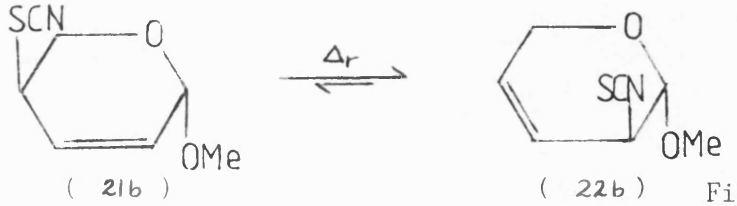


Figure 110

[Analogous treatment with sodium azide leads only to an equilibrium mixture of the two allylic azides, which is obviously not so

synthetically useful.]

The thiocyanate-isothiocyanate rearrangement route requires reaction of the freed allylic alcohol with a suitable reagent to establish a good leaving group which would allow direct S_N2 displacement by a thiocyanate nucleophile. This inversion, of course, immediately coverts the anomers from *syn* to *anti* (and *vice-versa*) (see Figure 111).

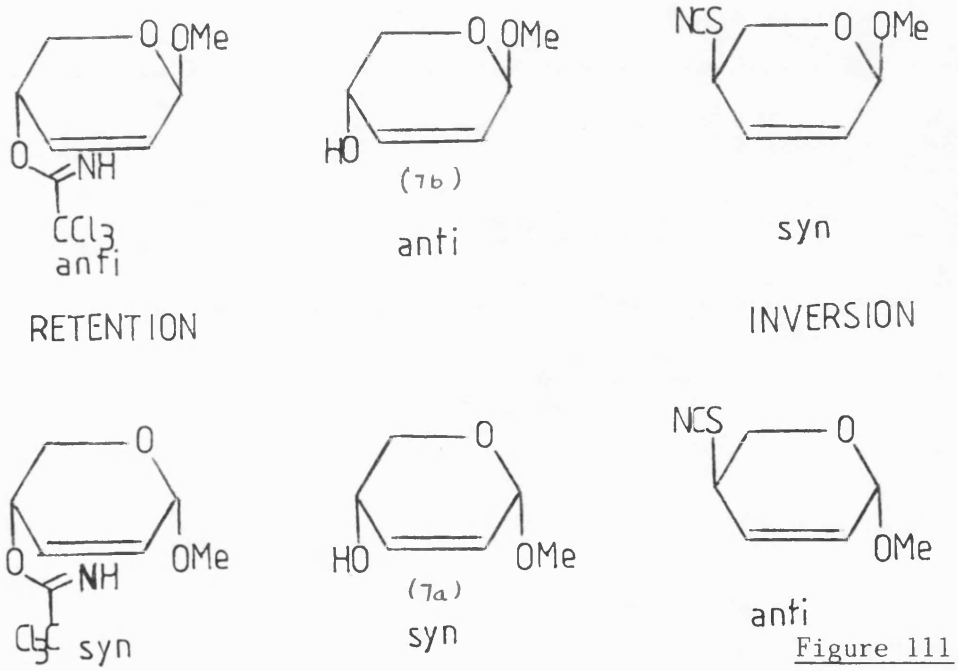


Figure 111

However, activation of the alcohol (6,7) under a variety of conditions proved to be difficult with respect to producing the desired active intermediate.

Attempts at tosylation[154] led to an impure product, which appeared to decompose on attempted purification and which, when used *in situ*, did not allow isolation of an unidentifiable product. Tosylation in the presence of potassium thiocyanate produced an activated tosylation agent which did not seem to produce a substituted product on further reaction. Extended reaction times to the tosylates (with TsCl. pyridine) proceeded to chlorine-substituted products (15,16),

presumably *via* an intermediate tosylate (*14*). Halogenated materials might have functioned as useful synthetic intermediates[155] had there not been evidence that the chloride nucleophilic substitution proceeded both directly (S_N2) and indirectly (S_N2').[156] This double bond regiochemistry was determined by considering the retro-dienic fragmentations visible (see Figure 112).

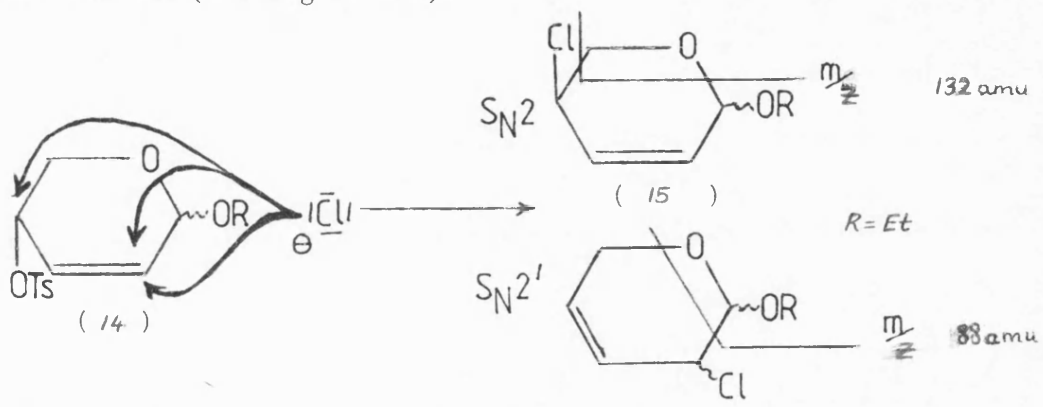


Figure 112

Triflation[157] was also unsuccessful, but indicated a possible difficulty in this synthetic approach, in that a rapid elimination reaction occurred (see Figure 113).

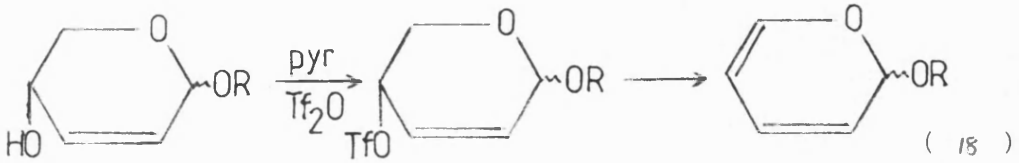


Figure 113

The elimination product, a 2-alkoxypyran (*18*), was unstable, undergoing an assisted ring-opening to an unsaturated aldehyde (*19*), which rapidly polymerised.[158] ^1H nmr analysis of the product from this reaction revealed an aldehydic proton (1H, 9·5 ppm, doublet, 8 Hz, coupling) and further unsaturation (see Figure 114).

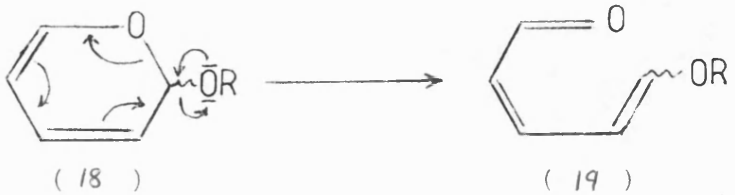


Figure 114

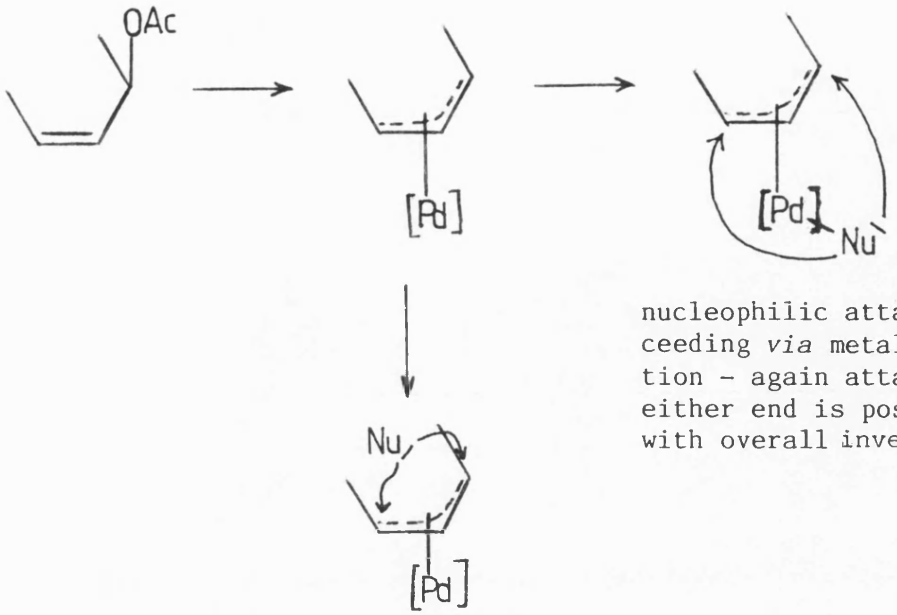
To attempt to circumvent the necessity of producing such an activated derivative of the unsaturated alcohols (6,7), it was decided to consider displacements of the allylic alcohols(6,7) or the allylic acetates(4,5).

These reactions require activation by the Mitsunobu conditions[152] (DEAD, PPh_3) or by BF_3.etherate complexation[159] in the case of alcohols(6,7), and by the formation of a π-allyl metal complex[160] in the case of the acetates(4,5).

Attempting a DEAD-mediated displacement of the allylic alcohols (6,7) with a thiocyanate nucleophile was unsuccessful, problems of low product recovery and the denticity of the nucleophile being encountered.

Attempted nucleophilic displacement of the BF_3-complexed alcohol led, instead, to an 'SCN' displaced product at the anomeric position, with the loss (in the nmr) of the anomeric alkoxy-group. The denticity of the ambident nucleophile seemed to be reversed in these conditions, the product appearing to be an isothiocyanate by analysis of the infra-red spectrum (broad peak at 2050 cm^{-1}).

The palladium-catalysed displacement of an allylic acetate[160] is a much more developed area of study, but had not been widely applied in the field of carbohydrate chemistry, due to the possible regio- and stereoisomerisation involved in the attack of a nucleophile on the intermediate palladium π-allyl complex (see Figure 115).



nucleophilic attack proceeding *via* metal complexation - again attack at either end is possible with overall inversion.

direct nucleophilic attack at either end of the allyl unit with overall retention.

Figure 115

One can therefore easily lose the inherent stereocontrol of carbohydrate chemistry using Pd-π-allyl intermediates.

The regiochemistry of such displacements seems governed by nucleophilic attack occurring at the end of the π-allyl system farthest from the electron-withdrawing substituents (see Figure 116).

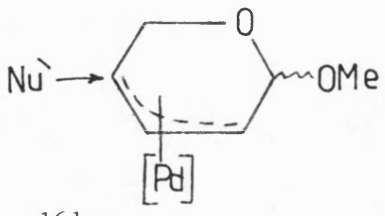


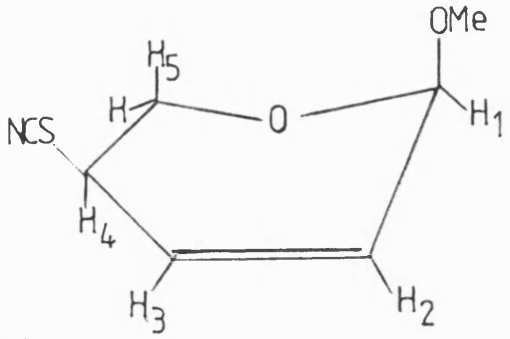
Figure 116

Baer and Hanna,[161] however, discovered that in the hexose series a C-4 allylic acetate could be replaced, in general, with overall retention at C-4 by a range of nitrogen nucleophiles, using tetrakis-triphenylphosphine [Pd(0)] as catalyst. No literature precedent could be found for such a reaction with the ambident thiocyanate nucleophile, and our meagre attempts to carry out the

transformation were unsuccessful.

The transformation was finally achieved by forming mesylate-derivatives (*20*)[162] (~70-80% yield) of the allylic alcohols (*7*) (by treatment with methanesulphonyl chloride and pyridine). These mesylate derivatives (*20*) were more readily formed than the tosylates (*14*) and less reactive than the triflates (*17*). They could be purified (freed from contaminating MsOH) by passage through silica, then readily displaced by potassium thiocyanate in acetonitrile. This displacement was reasonably clean and the product of direct S_N2 substitution[162] recovered in fair yield (>50%). These materials showed a thiocyanate peak in the infra-red spectrum (sharp peak at 2160 cm^{-1}) and a characteristic fragmentation for 2,3-unsaturation ($-CH_2O$) in the mass spectrum.

The ring conformations adopted were difficult to define by analysis of the ^1H nmr spectra but sufficient similarities were seen to suggest that the ring conformations were akin to those of the alcohols (7) and the acetates (*5*) (see Figure 117).



(21a)

H_1	4·88 ppm
H_2, H_3	5·99 ppm
H_4, H_5, H_5'	3·9-4·05 ppm
$-OCH_3$	3·45 ppm

(21b)

H_1	4·91 ppm
H_2, H_3	6·05-6·1 ppm
H_4	3·75 ppm
H_5	4·3 ppm
H_5'	4·0 ppm
$-OCH_3$	3·45 ppm

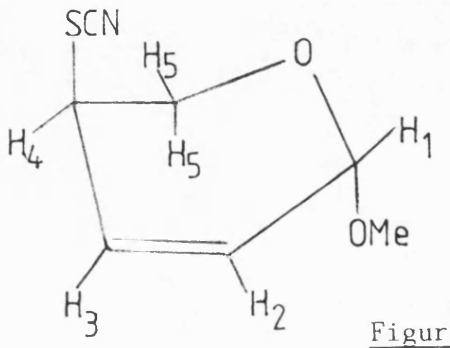
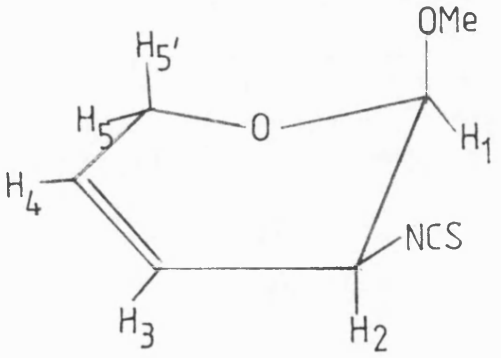


Figure 117

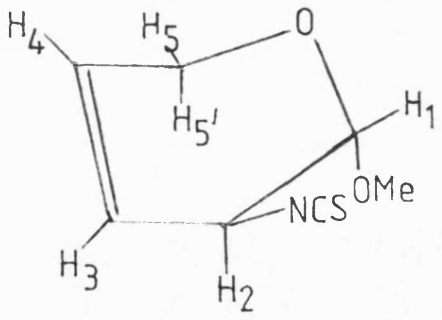
A little isothiocyanate material was recovered (broad peak around 2100 cm^{-1} in spectrum) though the structure of this product was not determined.

The thiocyanates (*21*) were then readily rearranged (>55% yield) to the corresponding isothiocyanates (*22*) (broad peak at 2050 cm^{-1} in the infra-red spectrum; characteristic fragmentation for 3,4-unsaturation [-OHCOMe] in the mass spectrum) by refluxing a solution in toluene for several hours[153] (see Figure 118).



(*22a*)	H_1	4·81 ppm
	H_2	4·34 ppm
	olefinic	5·70 ppm
	olefinic	5·92 ppm
	H_5	4·13 ppm
	$H_{5'}$	4·22 ppm
	OMe	3·56 ppm

(*22b*)	H_1	4·68 ppm
	H_2	4·02 ppm
	olefinic	5·76 ppm
	olefinic	6·00 ppm
	$H_{5,5'}$	4·22 ppm
	-OMe	3·51 ppm



[See COSY Spectrum in Appendix 3 for proof of regiochemistry]

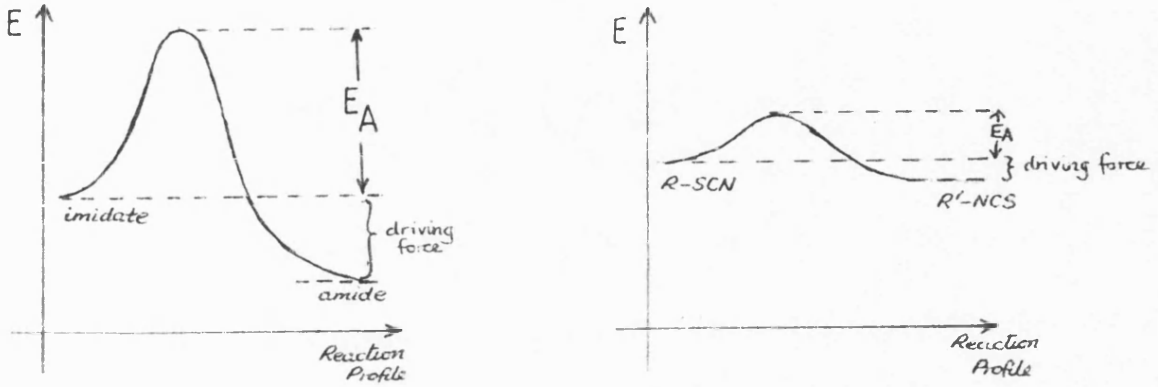
Figure 118

Because of the many instances of incompletely resolved signals, full analyses of the nmr spectra of the thiocyanates (*21*) and isothiocyanates (*22*) were not possible.

That displacement occurs with inversion, and rearrangement

occurs suprafacially, was essentially extrapolated from Ferrier's earlier studies.[153]

The activation energy for this rearrangement process is far smaller than that for the Overman rearrangement (see Figure 119).



Overman Rearrangement

Thiocyanate-Isothiocyanate rearrangement

Figure 119

Ferrier originally reported[153] that thermal rearrangement of 2,3-unsaturated *anti* compounds occurred markedly more rapidly than the isomerisation of the *syn* epimers, which, again, in order to react *via* the cyclic transition state, must adopt a high energy conformation with an unfavourable anomeric orientation. It was also observed that the nucleophilic displacements of mesylate-groups occurred more readily from the *syn*-isomer than from the *anti*-isomer. Whilst these effects were more noticeable for compounds where C_5 is substituted than for the pentoses studied here, minor differences in epimer reactivity were observed.

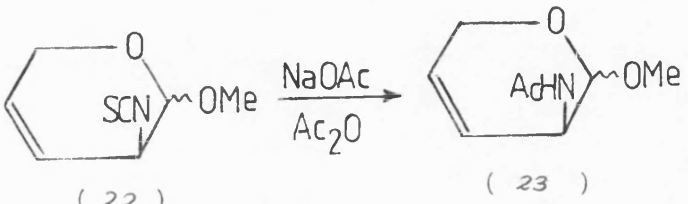
So the two rearrangement processes are truly complementary, both in terms of the epimer used with best efficiency, and with respect to the optical outcome of the C_2 chiral centre, which controls

Footnote:

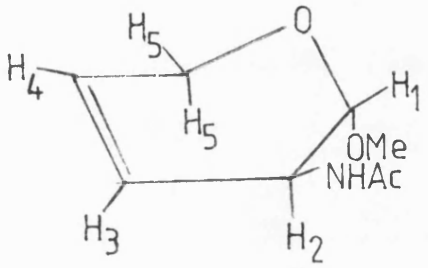
The thiocyanate/isothiocyanate rearrangement on the anomeric mixture (21) is complicated by increased difficulty of separation of the products.

the amino acid enantiomeric series synthesised.

The isothiocyanates (22) were then converted to the acetamides(23) (60%) (amide carbonyl stretch at 1655 cm^{-1} in the IR spectrum) by base-catalysed reaction with acetic anhydride.[153] (see Figure 120).



(22) (23)



Retro-dienic fragmentation characteristic of 3,4-unsaturation (-OHCOMe, 111) observable.

H_1	5·30 ppm
H_2	4·75 ppm
olefinic	5·5-5·6 ppm
olefinic	5·8-5·9 ppm
H_5	4·07 ppm
H_5	4·15 ppm
$-OCH_3$	3·49 ppm
$COCH_3$	2·01 ppm
NH	~5·8

Figure 120

The minor problems encountered in rearranging a *syn*-type material prompted a brief investigation into whether either rearrangment might be effected on material lacking the anomeric constraining factor, that is on the equivalent lactonic materials (see Figure 121).

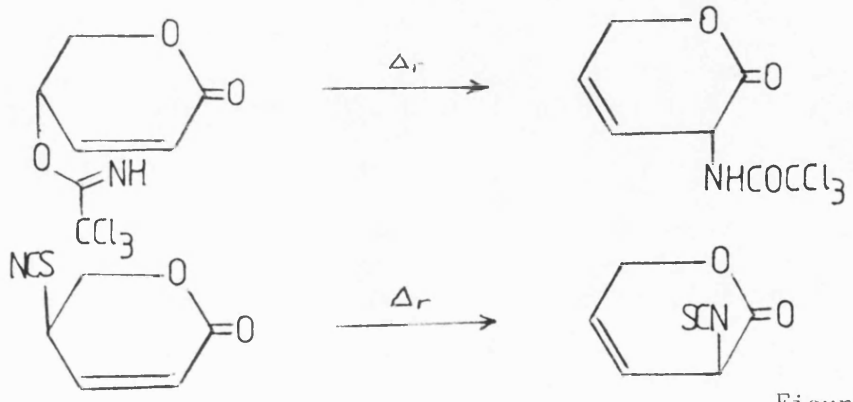


Figure 121

There were some problems intrinsic in this investigation, not the least of which were preparations of the substrates for rearrangement. In addition, the rearrangements themselves must proceed in such a way as to deconjugate the system, and whether the thermodynamic driving force for these rearrangements would be sufficient was an issue for debate.

Also it should be realised that the imidate functionality is capable of undergoing nucleophilic attack on suitable systems[163]* and may well undergo a Michael-type process rather than a rearrangement (see Figure 122).

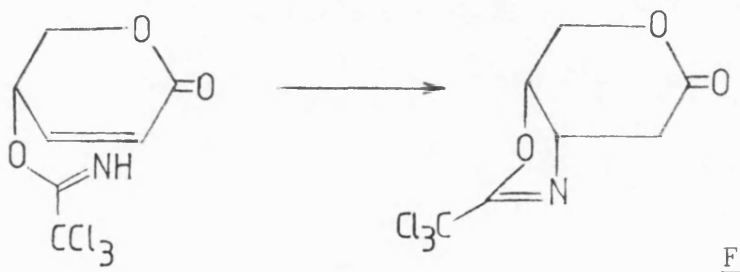
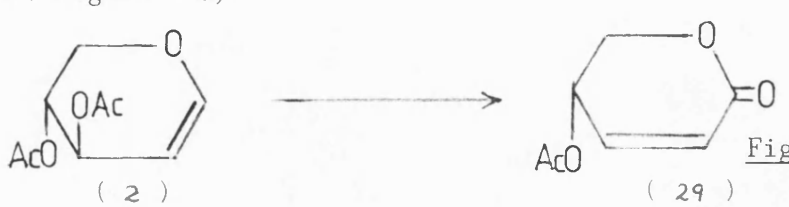


Figure 122

The first approach to be considered was to be the preparation, and subsequent derivatisation of the acetylated lactone (29); this substrate was to have been formed in an oxidative version of the Ferrier reaction,[164] but this approach was unsuccessful with a range of oxidants (mCPBA, H_2O_2, PCC), seemingly causing only decomposition (see Figure 123).

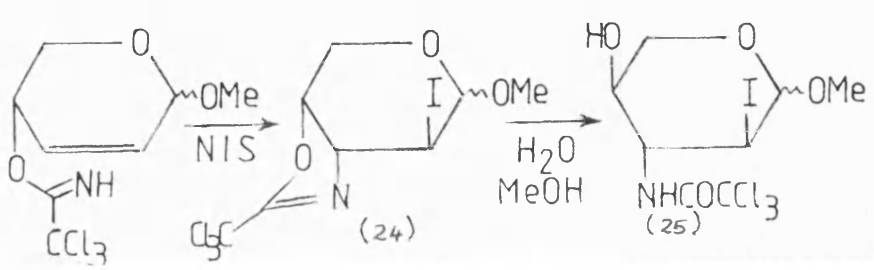


(2) (29)

Figure 123

* *Footnote:*

This inherent nucleophilicity of the imidate[163] *has been utilised in the preparation of 3-amino sugar derivatives* via *an iodocyclisation (with* N*-iodosuccinimide) process.*



(24) (25)

The desired lactone (29) was however synthesised less directly, *via* the glycosidic products of the Ferrier reaction (5), by acidic hydrolysis and oxidation (see Figure 124).

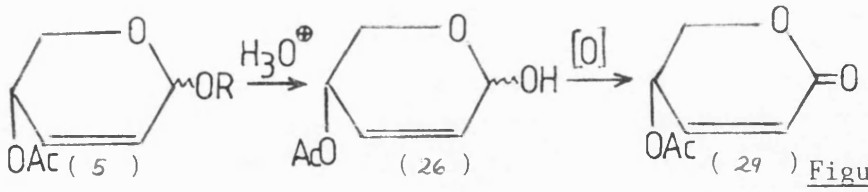
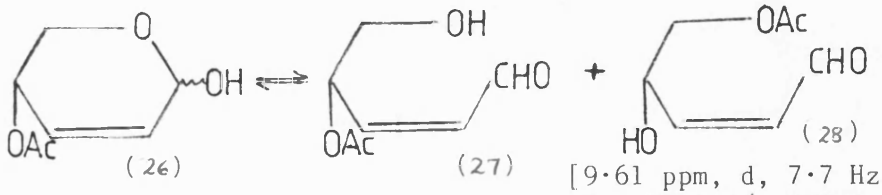


Figure 124

The glycosidic hydrolysis (Amberlyst 15 in H_2O) proceeded to give the lactol (26) as an anomeric mixture, which complicated the nmr spectra. The mass spectra showed the characteristic retro-dienic fragmentation for 2,3-unsaturation ($-CH_2O$, m/z 128) as well as the losses of H_2O (m/z 140) and HOAc (m/z 98).

This lactol (26) however exists in equilibrium with the tautomeric chain aldehyde (27) and a second aldehyde (28) formed by internal transesterification; these aldehydes may be recovered by column chromatography (see Figure 125).



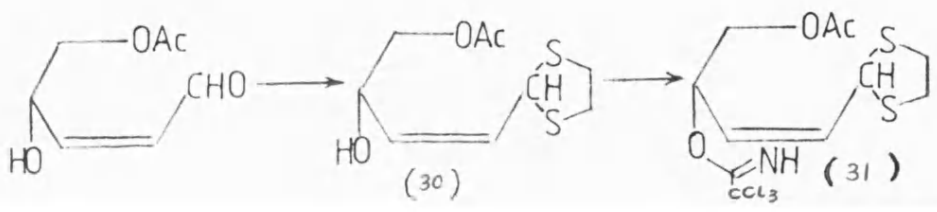
[9·61 ppm, d, 7·7 Hz. CHO] also M+1, m/z 159 in CI mass spectrum.

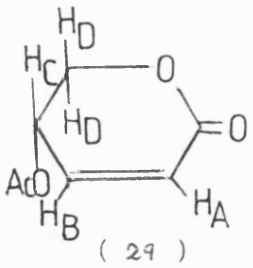
Figure 125

The lactol (26) was easily oxidised to the corresponding lactone (29) with pyridinium chlorochromate (see Figure 126).

Footnote:

> *The ability of the 2,3-unsaturated glycoside on acid-hydrolysis to show signs of ring-chain tautomerism was interesting. Either of these aldehydes might be useful in the synthesis of the* trans*-double bond isomer of the target aminophosphonic acid. Particularly, the following sequence of reactions was examined (see Experimental).*





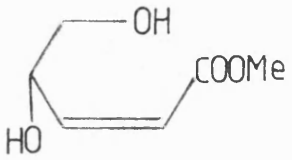
(29)

H_A	6·20 ppm	C_1	170 ppm
H_B	6·93 ppm	C_2	141 ppm
H_C	5·33 ppm	C_3	125 ppm
H_D's	4·52 ppm	C_4	69 ppm
$OCOCH_3$	2·12 ppm	C_5	62 ppm

	m/z
mass spectrum [M+1]	157
retrodienic for 2,3-unsaturation	126

Figure 126

However, the necessary deprotection of the allylic acetate in the presence of the lactone was not achieved, attempted transesterification of the acetate leading instead to a polar material, tentatively assigned on the basis of its mass spectra as the ring cleaved diol (32) (see Figure 127).



(32) $C_6H_{10}O_4$ m/z 146

(Acidic hydrolysis was not attempted.)

Figure 127

A second approach to likely rearrangement substrates might have been possible by prior conversion to an imidate (8) (see Figure 128).

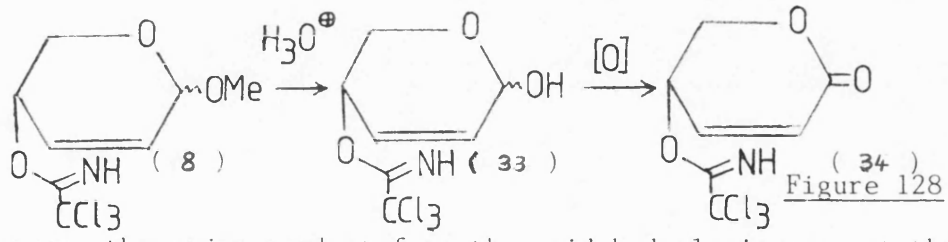
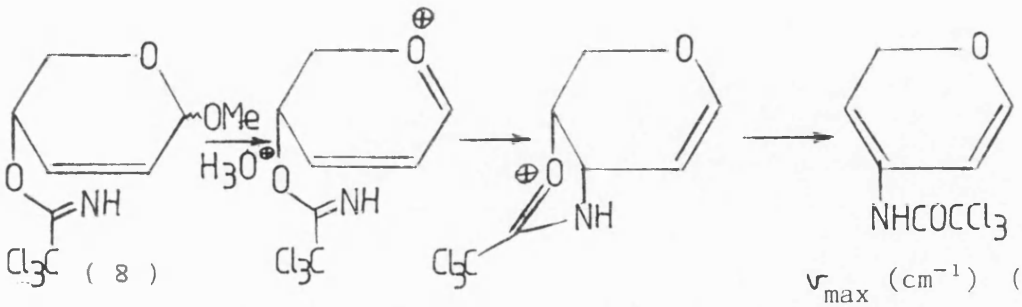


Figure 128

However, the major product from the acid hydrolysis was not the expected lactol (33); rather it appeared to be a dienic system (35) derived from the glycosidic material by overall dehydration (see

Figure 129).

This formation again relies upon the increased nucleophilicity of the imidate.



(8)

ν_{max}	(cm^{-1}) (35)
NH	3380
C=O	1715

No imidate N=H (1660 cm^{-1})

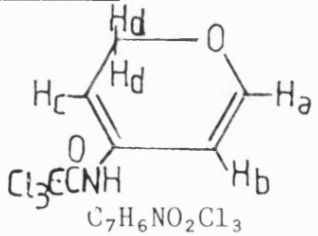
(See Footnote)

Figure 129

There was some evidence for lactol formation (-OH peak in IR spectrum at 3560 cm^{-1}, and loss of H_2O in CI mass spectrum) in this reaction, but not in synthetically useful quantities. Interestingly, no evidence for recovery of aldehydic chain tautomer was found here.

The thiocyanate derivative (21) might also be manipulated in a similar way (see Figure 130).

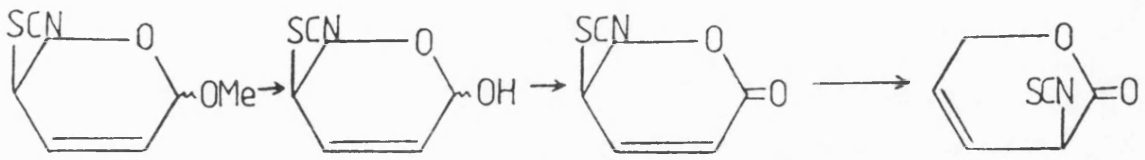
Footnote: Nmr data for the dienic amide:-



$C_7H_6NO_2Cl_3$

H_a	7·40 ppm	C_1	142·5 ppm
H_b	6·34 ppm	C_2	} 110·3, 107·7 ppm
H_c	6·29 ppm	C_4	
H_d	4·60 ppm	C_3	quaternary - not seen
NH	2·15 ppm	C_5	57·4

241 amu [M+1] in C.I. mass spectrum



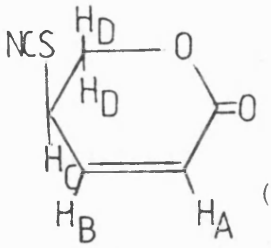
(21) (36) (37) (38)

Figure 130

The acidic hydrolysis (Amberlyst 15, H_2O, room temperature) was achieved in good yield (87%) and the infra red spectrum showed the presence of a thiocyanate functionality (2150 cm^{-1}, sharp) with a trace of the isothiocyanate material, and an alcohol functionality (3560 cm^{-1}).

The rearrangement in this material (36) appeared to be more facile than in the previous thiocyanates (21) studied, particularly the mass-spectra of this material showed the retro-dienic fragmentation of rearranged 3,4-unsaturated material (-HCOOH, m/z 111) along with molecular ion material and losses of H_2O and HSCN in the CI spectrum. The nmr spectra of this material were complicated by the presence of both anomers. (See Experimental Section for details.)

This lactol (36) was then oxidised with pyridinium chlorochromate[165] (low conversion - 52·4% yield, based on recovered starting material) to the corresponding lactone (37) (see Figure 131).



(37)

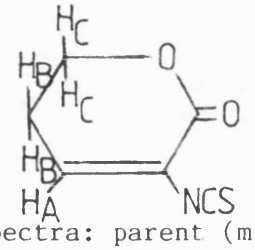
H_A	6·29 ppm	C_2	140·4 ppm
H_B	6·95 ppm	C_3	125·1 ppm
H_C	4·13 ppm	C_4	40·3 ppm
H_D	4·80, 4·66 ppm	C_5	69·8 ppm

IR: SCN, 2150 cm^{-1}; C=O, 1735 cm^{-1}

mass spectra: parent (m/z 155) and retro-dienic fragment for 2,3-unsaturation (m/z 125).

Figure 131

An attempt to rearrange this thiocyanate (37) to the deconjugated isothiocyanate (38) material thermally (by refluxing in toluene) was unsuccessful, seemingly producing rearranged, but conjugated material (though only in low yield) (see Figure 132).



(39)

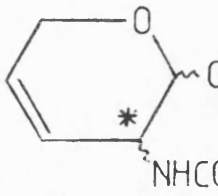
H_A	6·62 ppm	J_{AB}	4·8 Hz
H_B	2·61 ppm	J_{BC}	6·3 Hz
H_C	4·45 ppm		

mass spectra: parent (m/z 155) and 2,3-unsaturated retro-dienic (m/z 125)

[Other unidentified materials were produced here.]

Figure 132

Nevertheless two complementary rearrangement processes had been utilised to provide access to materials of known and opposite chirality of the type below (see Figure 133).



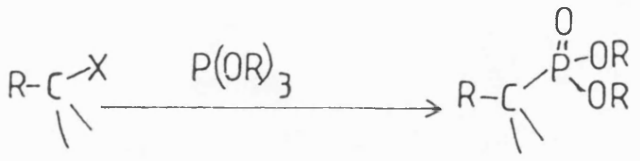
[R' = CH_3, CCl_3]

Figure 133

In order to further the synthesis it was necessary to achieve the synthesis of a lactone, derivatised in such a fashion as to allow the phosphorus chemistry to be successful. In this respect, halide-containing side-chains are unhelpful, since phosphorus nucleophiles

have a known affinity for such centres, undergoing Arbusov[166] and Perkow[167] reactions (see Figure 134).

Arbusov



Perkow

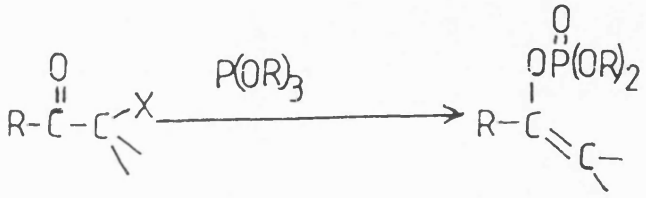


Figure 134

Thus it was necessary to have the facility to readily vary the amine side-chain functionality. This transformation was achieved directly by utilising the ability of the trichlorocarbon centre to act as a leaving group, or indirectly, by completely freeing the amine and reprotecting (see Figure 135).

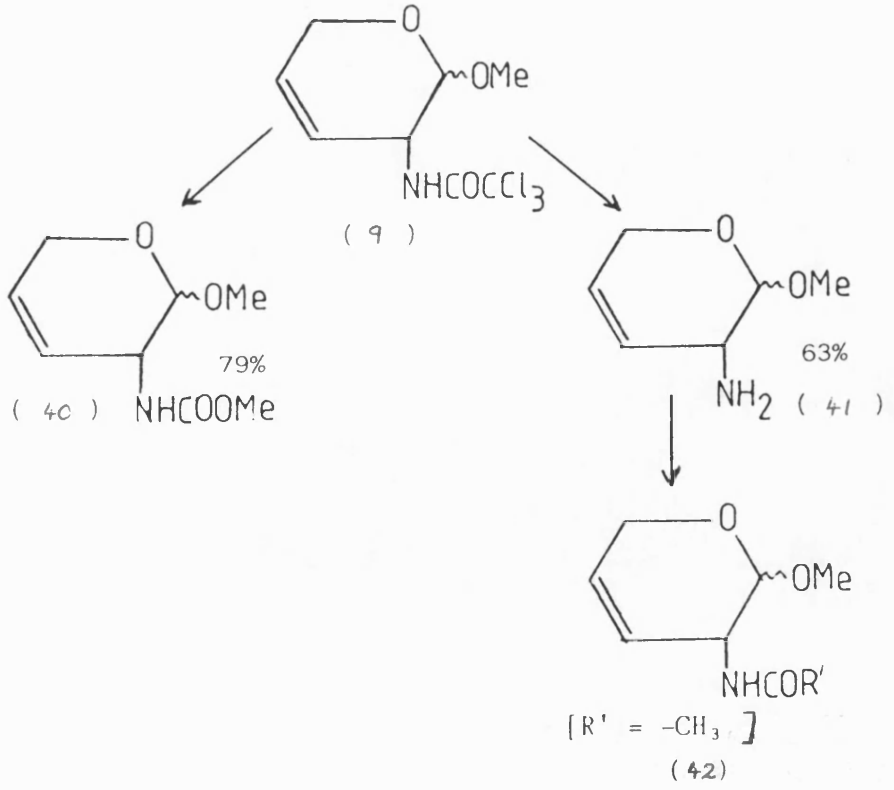
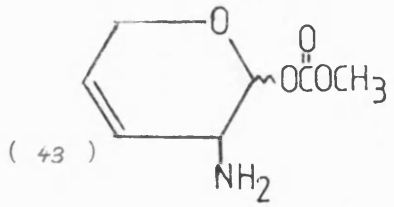


Figure 135

This alcoholytic conversion of the trichloroacetamide (9) directly to the carbamate (40) was a convenient method of changing the side-chain protection, whereas the alkaline hydrolysis to the free amine (41) allowed reprotection with any suitable side-chain. It should be remembered that the aminophosphonic acid is the C-terminus of the Plumbemycin tripeptides; thus dipeptidic material must sometime be coupled through this amine functionality.

It was interesting that a side-product from the trichloroacetamide (9) to methylcarbamate (40) alcoholysis, caused by a work-up which became acidic, was the suspected amino carbonate (43), (see Figure 136) which could be further manipulated.



(43)

Figure 136

This product was formed, presumably, through the ability of the C-2 amide (or carbamate) functionality to participate in reactions at the anomeric centre (see Figure 137)

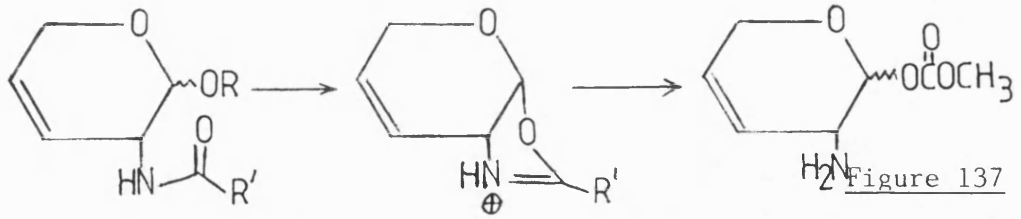
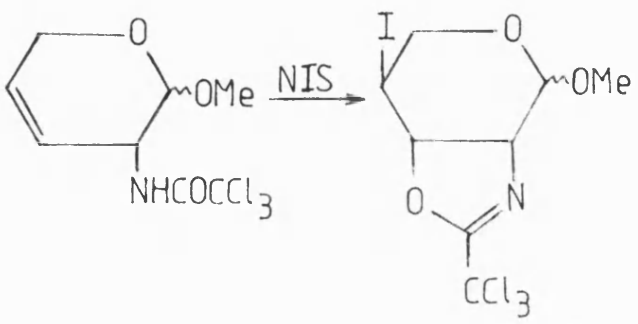


Figure 137

and suggests its ability to participate generally. Indeed iodocyclisation of the trichloroacetamide (9) was observed (see Figure 138), tentatively, on reaction with N-iodosuccinimide.



$C_8H_9NO_3Cl_3I$

(399 amu)

CI m/z 368, -MeOH

Figure 138

Having achieved the ability to vary the side-chain functionality it remained to convert the glycosidic materials to the corresponding lactones (see Figure 139).

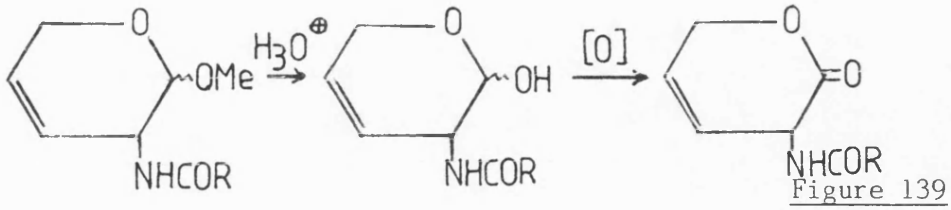


Figure 139

The 3,4-unsaturated glycosides were simply hydrolysed to the lactols in aqueous acid, though problems of reproducibility were encountered when dealing with the trichloroacetamide side-chain protecting group, probably caused by the acid-lability of this group (see Table 140).

Table 140

R	% yield	Conditions	
$-CCl_3$	77·0	2N HCl, Δr, <3 hours	(45)
$-CH_3$	83·8	2N HCl, r.t., 24 hours	(46)
$-OCH_3$	81·9	2N HCl, r.t., 24 hours	(47)
-NCS	not possible*	2N HCl, Δr, 1 hour	(48)

Interestingly, unlike in the hydrolysis of the 2,3-unsaturated glycoside, there was no sign of the 3,4-unsaturated materials undergoing ring-chain tautomerism, and no aldehydic material was evident. Presumably, this difference is due to the *cis*-double bond constraining the ring more completely, or, rather, making any chain tautomeric

Footnote:

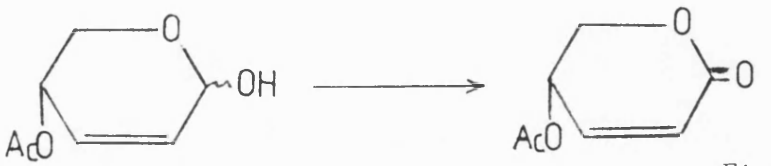
The hydrolysis of the isothiocyanate glycoside (22) was unsuccessful; instead an unidentified material lacking the thiocyanate/isothiocyanate functionality was recovered; the IR spectrum revealed a carbonyl stretch (1690 cm^{-1}).

allylic alcohol adopt a conformation which favours re-closure. The 2,3-unsaturated material on hydrolysis gives instead a homoallylic alcohol, which is more flexible and less prone to re-closure.

The final step in the synthesis of the desired lactones is, of course, an anomeric oxidation.[168] There are a large number of reagents available for such an oxidation, but classical methods such as the use of bromine water[169] were ignored since the double bond would be susceptible to saturation. Similarly, the Oppenauer oxidation[170] was not considered since the conditions employed would have the unwanted side-effect of promoting double bond conjugation.

Thus, it was necessary to determine oxidative processes which do not suffer from such disadvantages.

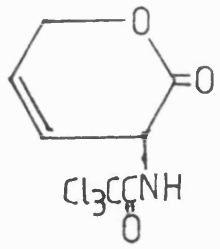
Remembering the success of a pyridinium chlorochromate oxidation[165] of the lactol (26) to the lactone (29) (see Figure 141) this was the first reagent tried.



(26) (29) Figure 141

On a small scale this method seemed to be successful (IR analysis of the crude material showed loss of the alcohol at 3600 cm^{-1} and formation of a shoulder in the carbonyl region ~1760 cm^{-1}) but further study suggested that the oxidation was complicated by low consumption of starting material, by the formation of aldehyde side-products (minor, 8·96 ppm, doublet, 10 Hz) possibly by oxidation of the double bond, and probably by the participation of the C-2 functionality in the oxidative process. Lactonic material could be recovered, though (27·7%, 50·4% based on recovered starting material,

R = CCl_3) (see Figure 142).



	NH 7.63ppm	lactone C=O	167ppm
	olefinic 6.20ppm	C=O	162ppm
	olefinic 6.15ppm	olefinic	126ppm
	C_2H , C_5Hs 4.9-5.0ppm	olefinic	125ppm
		C_5	68ppm
IR	C=O 1750 cm^{-1}	C_2	50ppm

Figure 142

A system using pyridinium dichromate[171] (PDC - 3 eq^v - molecular sieves- HOAc catalyst) was then tried, with similar success; again the yield of lactonic material (49) was only modest (28·2%; 52% on rec. sm.) oxidation being complicated by formation of products of C-2 functionality participation, tentatively assigned the structures shown below (see Figure 143) (see Experimental section).

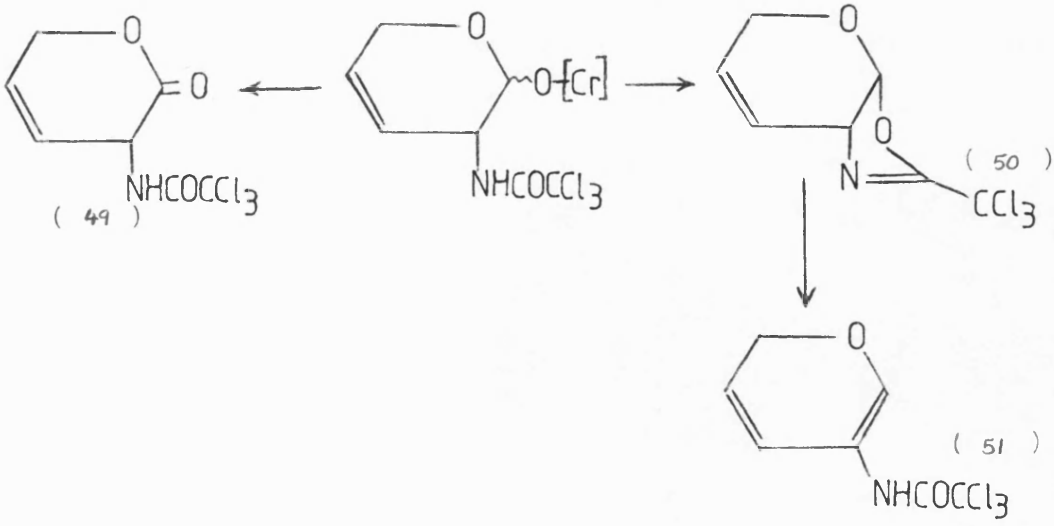
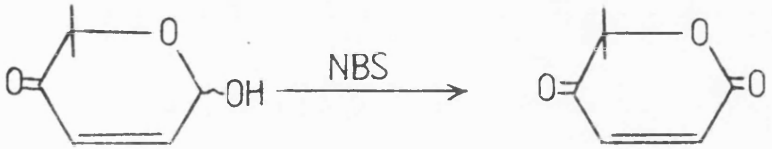


Figure 143

A Jones oxidation[172] (CrO_3/H_2SO_4 in acetone) was also attempted, but the outcome was hard to divine since recovery of the rather water-soluble substrates was difficult.

The use of *N*-bromosuccinimide[173] for the conversion of the lactol (*52*) to the conjugated lactone (*53*) had been reported (see Figure 144).



(52) (53) Figure 144

However, application of the conditions used to the substrate lactols here caused extensive vinylic and anomeric bromination (see Figure 145).

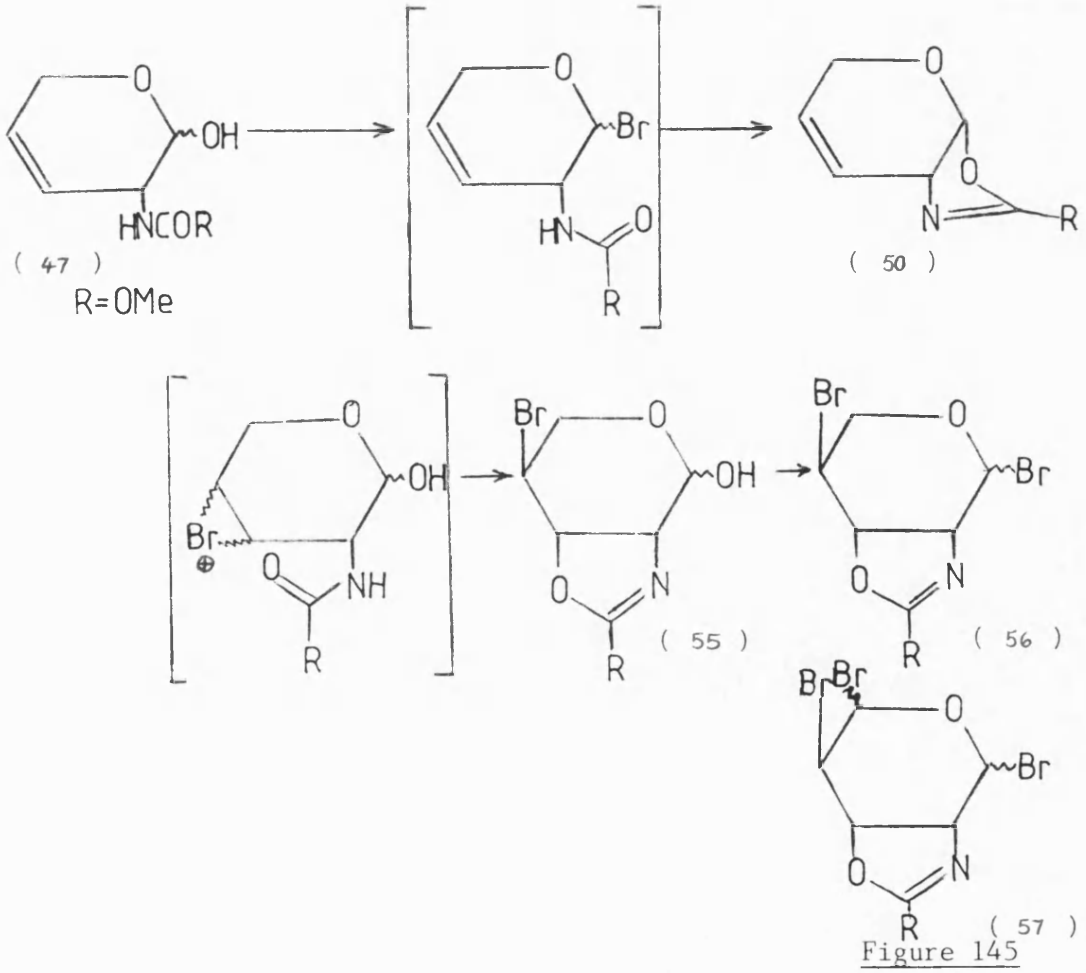
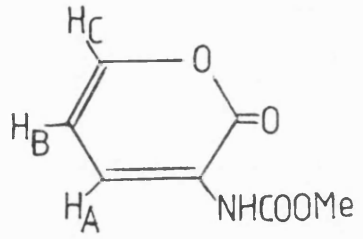


Figure 145

Similar problems might have been anticipated with *N*-iodosuccinimide,[174] however this material did produce the desired lactonic product (in low yield, ~20%). Here the oxidation was complicated by the recovery of an over-oxidised pyrone product (58), probably caused by initial allylic iodination, and elimination (see Figure 146).



(58)

H_A 7·23 ppm

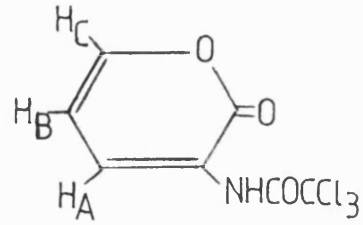
H_B 6·30 ppm

H_C 7·87 ppm

$[M]^{\bullet+}$ 169

Figure 146

Similarly, the use of excess activated manganese dioxide[175,176] caused exclusive formation of this pyronic product (59), by direct dehydrogenation (see Figure 147).*



(59)

H_A 7·35 ppm

H_B 6·39 ppm

H_C 8·23 ppm

$[M]^{\bullet+}$ 255

Figure 147

Another ingenious oxidative system reported involved the metal-catalysed formation of an intermediate peroxide,[177] which is decomposed by acetylation in pyridine to yield lactonic material by elimination (see Figure 148).

Footnote:

It should be noted that batches of MnO_2 seemed variable Also the reported parallel efficacy of MnO_2 adsorbed on carbon[176] in oxidations was not observed here.

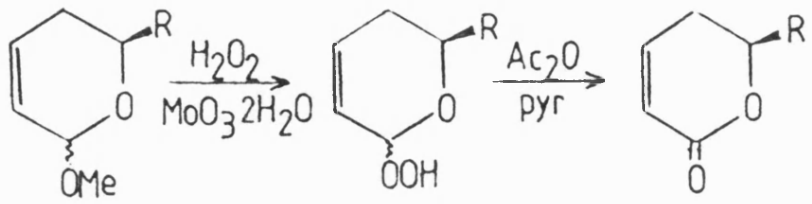


Figure 148

However, attempts to utilise this system with the substrate lactols here were unsuccessful; the intermediate peroxides not being formed.

The reported ability of the high oxidation state ferrate ion[178] (Fe VI) to cause selective oxidation of secondary alcohols was investigated, but a system involving potassium ferrate (K_2FeO_4, $CuSO_4$, basic alumina) was found to be inactive here.

Similar inactivity was found with a batch of Fetizon's reagent system,[179] comprising adsorbed silver carbonate on Celite.

An attempt to effect the oxidation by catalytic dehydrogenation[180] was made (utilising reduced Adams' catalyst, in acidic solution, and oxygen) but this reaction did not proceed to completion readily; it appeared that an equilibrium was established, again possibly relying on the participation of the C_2 functionality in acidic solution (see Figure 149).

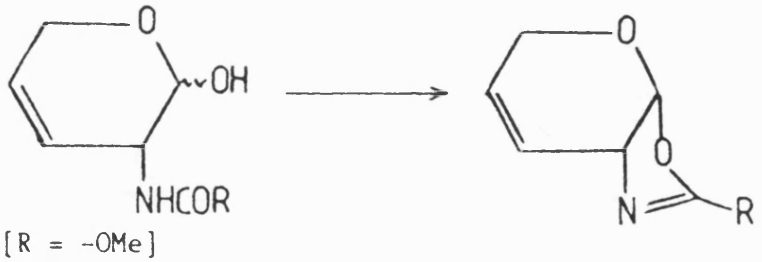


Figure 149

The most successful means of transforming the lactol substrates to the lactones discovered was the system involving dimethylsulphoxide[181] activated towards reduction by acetic anhydride. This

process was also complicated by the formation of side-products (namely an anomeric acetate and conjugated lactonic material) (see Figure 150).

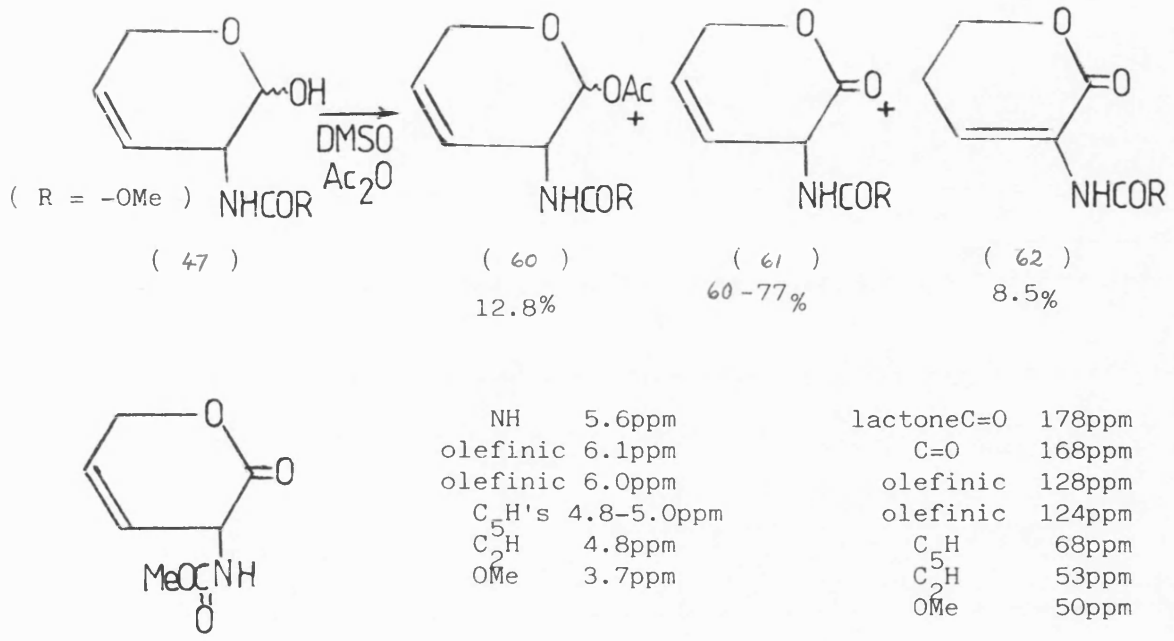


Figure 150

The acetate is an obvious by-product of the active oxidising agent, which is also an active acylating agent.

However the yield of the lactone could be made respectable (~60%) by careful control of the reaction conditions, acetylation seeming to be favoured where the active DMSO species reacted with the alcohol at approximately ambient temperature. However, when the initial reaction was performed at lower temperature the intermediate leading to oxidation predominated, so oxidation was the major outcome (see Figure 151).

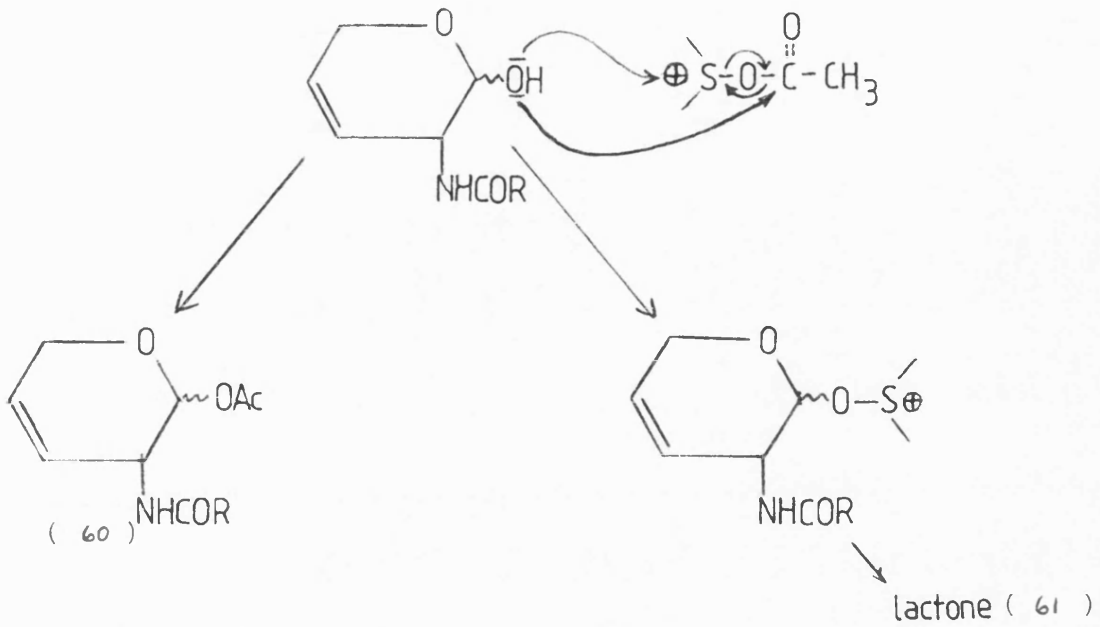


Figure 151

In addition, any acetate product formed can be readily reconverted to the lactol (70·8%) by acidic hydrolysis (2N. HCl, r.t., 3-4 hrs.).

Other DMSO-activated reagent systems[181] have not been studied; many of these, in any case, either suffer from this reversal from oxidising agent to active protecting agent, or, as in the case of the Swern system (comprising DMSO/oxalyl chloride) the intermediate has to be decomposed by addition of a basic reagent (eg NEt_3) which might promote further conjugation.

Other interesting oxidation systems have been reported to have utility with carbohydrate substrates, particularly Barton's pentavalent bismuth system,[182] the pentavalent iodine species reported by Dess and Martin[183] and a DEAD-mediated system reported by Mitsunobu,[184] but these were not studied here. Similarly, enzymic oxidations were not attempted.[185]

Nevertheless, the synthesis of the target lactone had now been

achieved. The chiral integrity of such lactones had been determined by an nmr experiment, involving complexation to a chirally-modified lanthanide reagent. No diastereomeric doubling-up of signals was observed. This result might have been anticipated, since any mechanism for 'racemisation' would probably involve conjugation, and conjugation of course involves loss of chirality. The lactones were still optically active.

Now the incorporation of the phosphonate moiety into the lactone must be examined. This is, even conceptually, a not inconsiderable challenge. First, this transformation was attempted by a direct reaction, employing a nucleophilic phosphorus species.[125] However, the lactone substrates have a number of centres which are sensitive to the incorporation of a phosphorus nucleophile (see Figure 152).

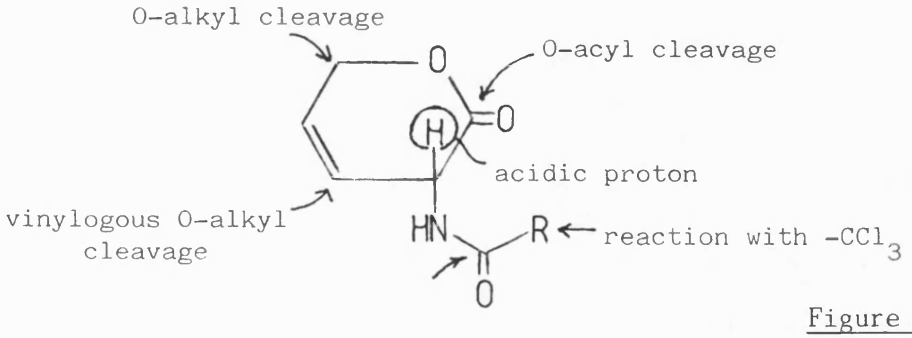


Figure 152

and, again, the basicity of the nucleophilic species may cause problems in maintaining the regiochemistry of the double bond, conjugation being a constant threat.

The first reaction attempted was to simply react the trichloroacetamide-protected lactone (49) (essentially the *parent* substrate) with a trialkyl phosphite [$P(OMe)_3$, $P(OEt)_3$] at elevated temperature and attempt to isolate Arbusov products of *O*-alkyl cleavage;[125,165] that is, phosphonates of the desired type (see Figure 153).

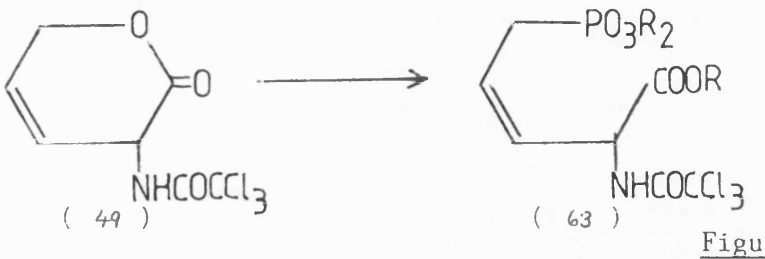


Figure 153

As suspected, this process was complicated by a competitive process occurring in the side-chain (see Figure 154), but *not* the Perkow reaction expected: though ring-cleaved materials are evident.

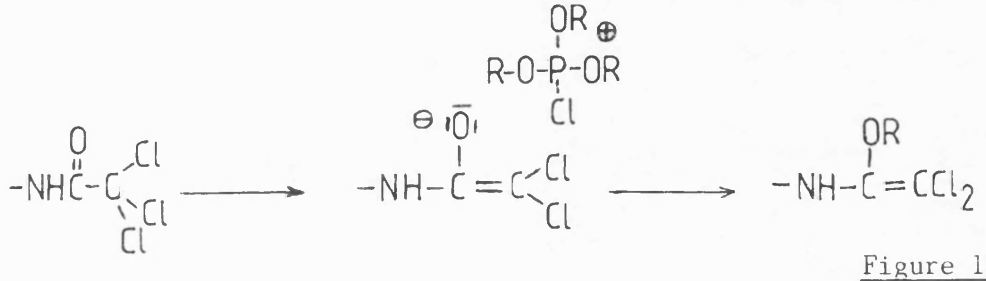


Figure 154

The structures of products from this reaction (determined by gc-ms analysis) include the product of Arbusov-reaction and methylation (64); Arbusov-reaction and H-abstraction (65) and also a ring cleaved product from (66) (see Figure 155).

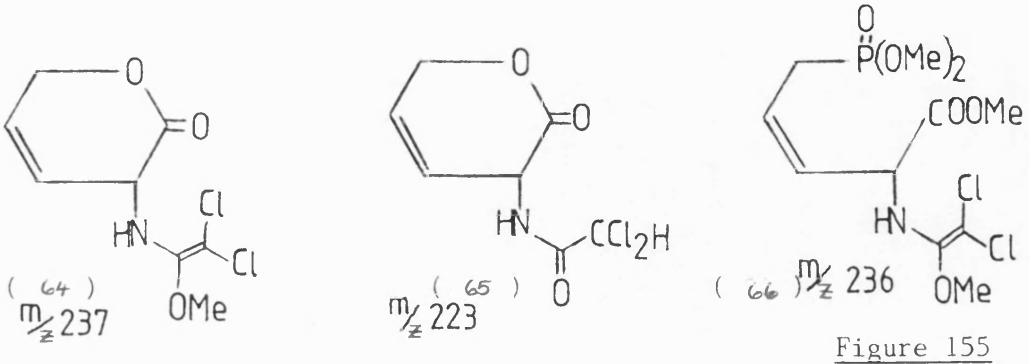
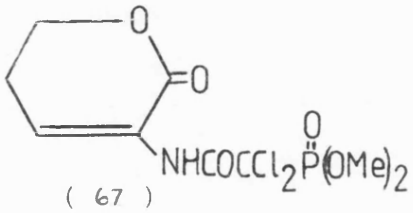


Figure 155

The trichloroamide side-chain was therefore shown to be a complication in reactions with phosphorus nucleophiles. A Michaelis-Becker[125] [NaP(O)(OMe)$_2$] type reaction on the trichloroamide-protected

lactone (49) was similarly complicated by reaction at the side-chain. This product was tentatively assigned to have the structure (67) by consideration of the mass spectrum (see Figure 156).



(67)

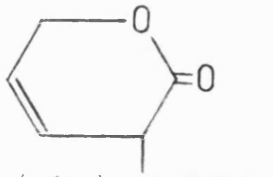
$C_9H_{12}NO_6PCl_2$ - 331 amu

[M+1] m/z 332

retro-dienic m/z 301

Figure 156

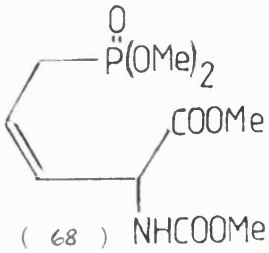
Therefore similar reactions were carried out on lactonic substrates bearing a less intrinsically reactive side-chain protecting group, namely the methylcarbamate formed by treatment of the parent lactone (49) with basic methanol (see Figure 157).



(61)

Figure 157

Here the Arbusov reaction with trimethylphosphite was very slow (unopened lactonic material remaining after extended periods - 10 days - of reflux) with conjugation predominating. Polar products of the correct isomeric mass were also detected by mass spectral analysis (see Figure 158).



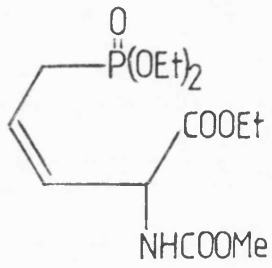
(68)

$C_{10}H_{18}NO_7P$ - 295 amu

[M+1] m/z 296

Figure 158

Further elevation of the reaction temperature achieved by using triethylphosphite as the solvent caused the reaction to proceed more efficiently, the lactone being consumed in approximately thirty hours at reflux. Now products from the reaction included some conjugated lactonic material (~8%) and also products which by gc-ms analysis appeared to be isomeric with the desired ring-opened phosphonate material (69) (see Figure 159).



(69)

Figure 159

Isomerisation might be envisaged as occurring by conjugation, either to the carboxylic centre or to the phosphonate, and due to the extended high temperature conditions of the reaction, there is also the possibility of the material undergoing *cis-/trans*-isomerisation.*

Separation of these isomeric materials proved to be difficult to achieve, but analysis of the available data suggested that

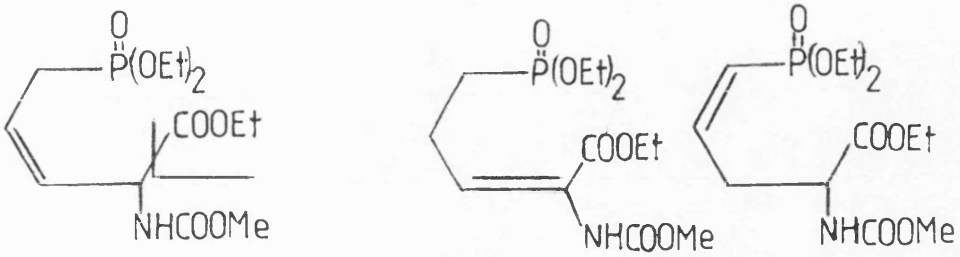
i) not all the materials were conjugated with the carboxylic centre since the mixture of materials was still optically active.

ii) the mass spectra of the isomeric materials (gc-ms)

Footnote:

The data for these isomers could be accounted for without requiring the product formed by vinylogous lactone cleavage, which would require all 3 olefinic protons available in the ^1H nmr spectrum.

suggested evidence for partial conjugation to the carboxyl-centre by consideration of the fragmentations available (see Figure 160).



loss of COOEt evident

COOEt loss is not observed

Figure 160

iii) even after partial HPLC purification (to a single peak) this material still showed evidence of isomerisation in the ^1H nmr spectrum. These isomers were tentatively assigned by correlation with material previously characterised:-

APPA - the natural aminophosphonic acid[122] (in D_2O, 100 MHz)

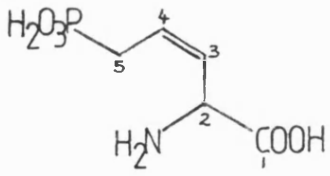


Figure 161

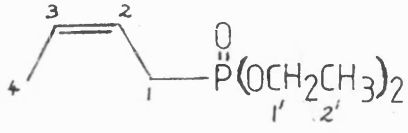
C_5H 2·72 ppm, d of d, 2H, 8·4, 23 Hz

C_2H 4·81 ppm, d, 1H, 9·5 Hz

C_3H 5·64 ppm, d of t, 1H, 5·1, 9·5 Hz

C_4H 6·12 ppm, m, 1H

material synthesised by Salzer *et al.*[186]



(in C_6D_6, 200 MHz)

Figure 162

C_1H 2·49 ppm, d of d, 2H, 6·25, 22 Hz

C_2H 5·42-5·67 ppm, m, 1H

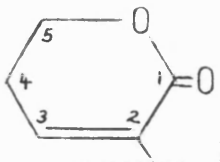
C_3H 5·42-5·67 ppm, m, 1H

C_4H's 1·48 ppm, d of d, 3H, 4·5, 4·0 Hz

C_1^1H 3·86-4·01 ppm, m, 4H

C_2^1H 1·05 ppm, m, 6H

conjugated material



(62) MeOOCNH

Figure 163

C_3H 7·18 ppm, t

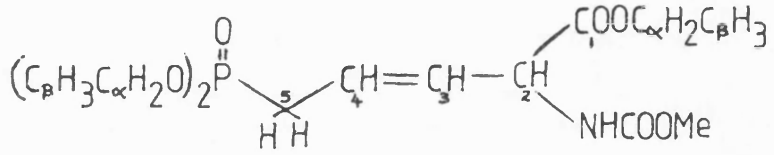
C_4H's 2·58 ppm, t of d

C_5H's 4·44 ppm, t

-OMe 3·74 ppm

Figure 163

So, the isomers were assigned as below (without consideration of double bond geometry):-



(69)

C_2H 4·88 ppm

C_3H 5·4 ppm

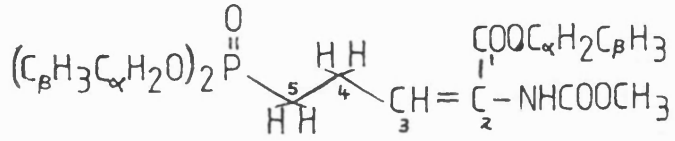
C_4H 5·8 ppm

C_5H 2·6 ppm

$-OCH_3$ ~3·7 ppm

CαH's 4·1-4·3 ppm

CβH's 1·3 ppm



(70)

C_3H 6·53 ppm

C_4H's 2·2 ppm

C_5H's 2·6 ppm

OCH_3 ~3·7 ppm

CαH's 4·1-4·3 ppm

CβH's 1·3 ppm

$-OCH_3$ ~3·7 ppm

CαH's 4·1-4·3 ppm

CβH's 1·3 ppm

Figure 164

Footnote:

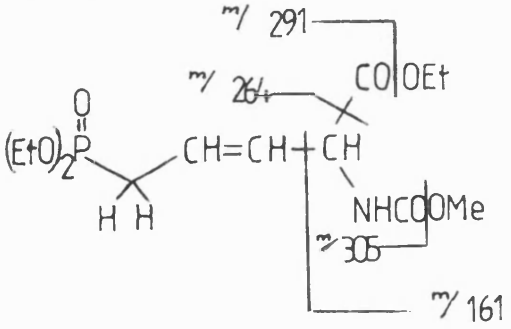
Two roughly equivalent side-chain methoxy singlets are visible.

Similarly, the ^{31}P nmr also shows evidence of two isomeric phosphonates (31·1, 26·0 ppm), supporting the regiochemical assignment of the unsaturation (see Figure 165).

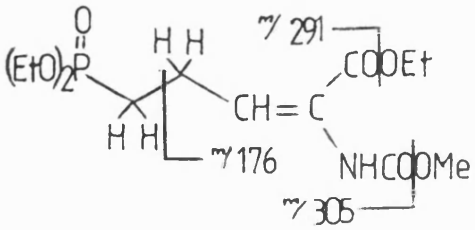
	^{31}P nmr
$H_3C - HC = HC - H_2C - P(=O)(OEt)_2$	27·8 ppm[186]
$H_3C - H_2C - P(=O)(OEt)_2$	31·8–32·8 ppm[187]

Figure 165

Analysis of this mixture by combined gas chromatography/mass spectroscopy similarly revealed these two isomers, with double bond regiochemistries also capable of assignment in the same fashion (see Figure 166)



(A)



(B)

No strong -COOEt loss

Figure 166

The fragment (m/ 176) effectively rules out both the isomer caused by conjugation to the phosphonate and that resulting from vinylogous lactone cleavage.

The stereochemistry of the double bond in the unconjugated material (A) was best determined by consideration of the ^{13}C nmr

spectrum of the mixture, and again by correlation with previously-assigned materials. However, though its structure was closest to the *cis* -material, this is not categoric proof of structure, particularly since assignment of each signal to either isomer was difficult.

APPA - the natural aminophosphonic acid[122]

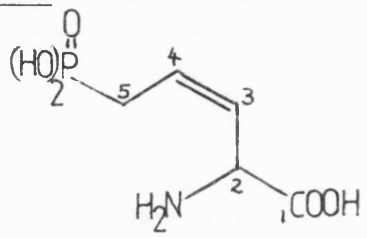
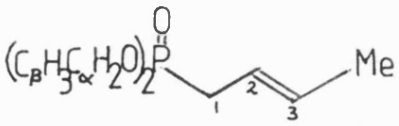


Figure 167

	δ(ppm)	Jp-c (Hz)
C_5	29·3	127
C_4	132·9	11
C_3	123·5	12
C_2	51·5	-

material synthesised by Salzer *et al.*[186]



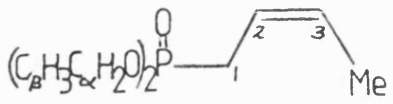
trans-

Figure 168

	δ(ppm)	Jp-c (Hz)
C_1	31·2	140·0
C_2	121·0	22·0
C_3	129·8	14·5
Me	18·1	2·0
Cα	61·5	6·5
Cβ	16·7	5·5

Footnote:

Determination of the stereochemistry of the double bond was not readily achieved from consideration of the ^1H nmr, since individual coupling constants could not be analysed.

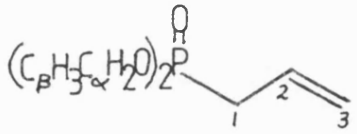


	δ(ppm)	Jp-c (Hz)
C_1	26·0	140·0
C_2	120·1	12·5
C_3	127·8	14·5
Me	12·9	1·5
Cα	61·5	6·5
Cβ	16·7	5·5

cis-

Figure 169

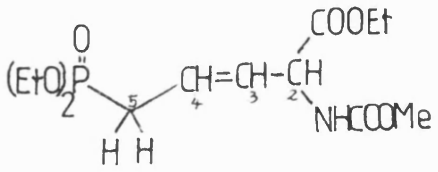
material synthesised by P.M. Winton[188]



	δ(ppm)	Jp-c (Hz)
C_1	32·0	138·6
C_2	129·2	22·0
C_3	119·2	14·3
Cα	61·7	6·3
Cβ	16·7	5·5

Figure 170

So the isomers were assigned as below:-



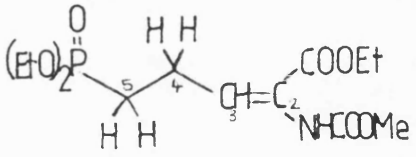


Figure 171

δ(ppm), Jp-c

C_2 - 52·6 ppm	C_2 - quaternary, not visible
C_3 - 129·5 ppm, 15·4 Hz	C_3 - 123·0 ppm, 11 Hz
C_4 - 133·5 ppm, 11·1 Hz	C_4 - 21·5 ppm, 4·4 Hz
C_5 - 30·2 ppm, 141·8 Hz	C_5 - 24·0 ppm, 141·0 Hz

-OMe, 55·402, 52·418 ppm

Phosphonate ethyl ester	Cα	62·1 ppm	6·6 Hz
		61·8 ppm	6·6 Hz
	Cβ	16·4 ppm	4·4 Hz
ethyl ester	CH_2	61·7 ppm, 61·5 ppm	
	CH_3	14·15 ppm, 14·05 ppm	

Attempts to boost the efficacy of this Arbusov reaction by inclusion of catalytic reagents have, so far, proved useless.

For instance, analysis of this Arbusov process suggested an autocatalytic mechanism[166] (see Figure 172).

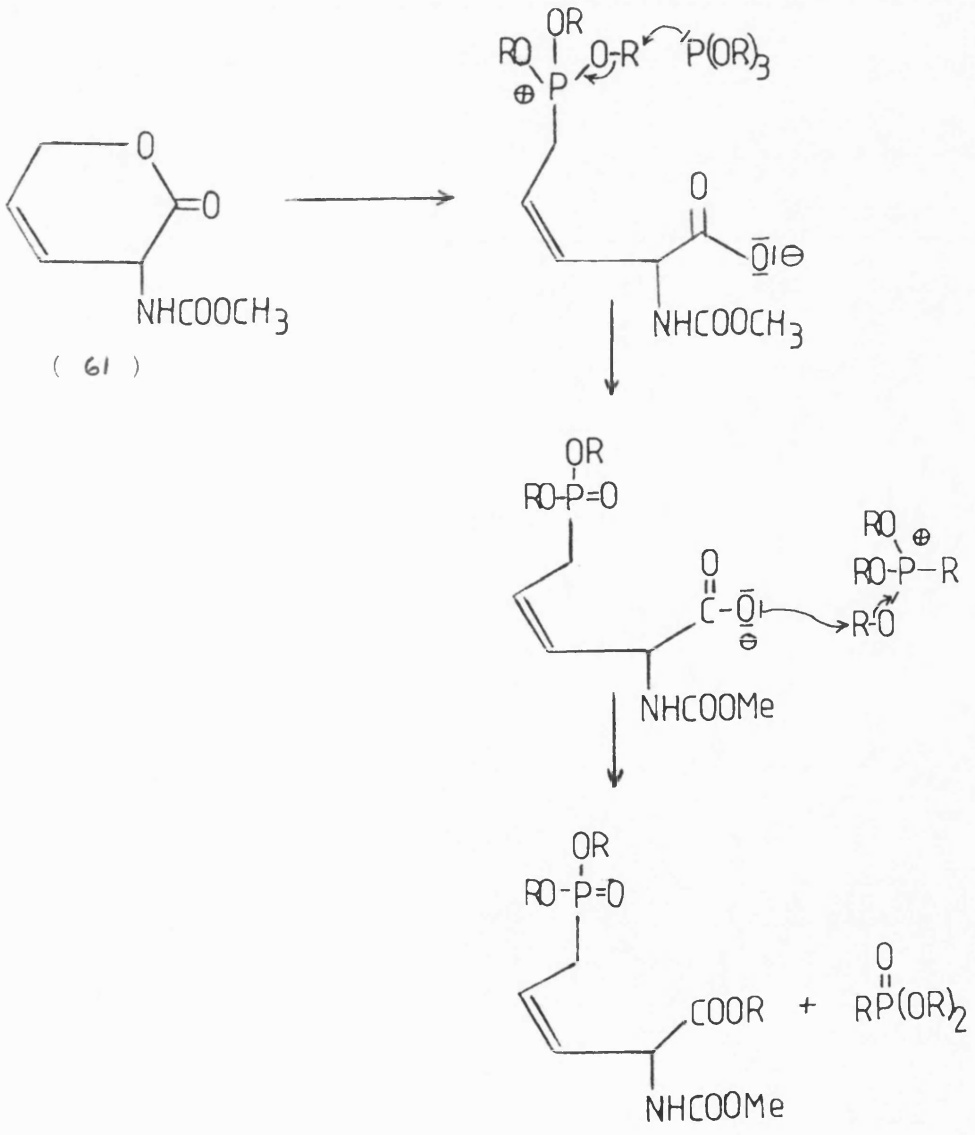


Figure 172

Indeed, ^1H nmr analysis of the solvent after the reaction showed definite indications of this process having occurred.

Solvent prior to reaction: 3·4 ppm, doublet, 12 Hz, $P(OMe)_3$

Solvent after the reaction: increase of doublet at 1·4 ppm, 18 Hz, $MeP(OMe)_2$

It was suggested that addition of a catalytic quantity of an active methylating material to the mixture might accelerate the reaction (see Figure 173).

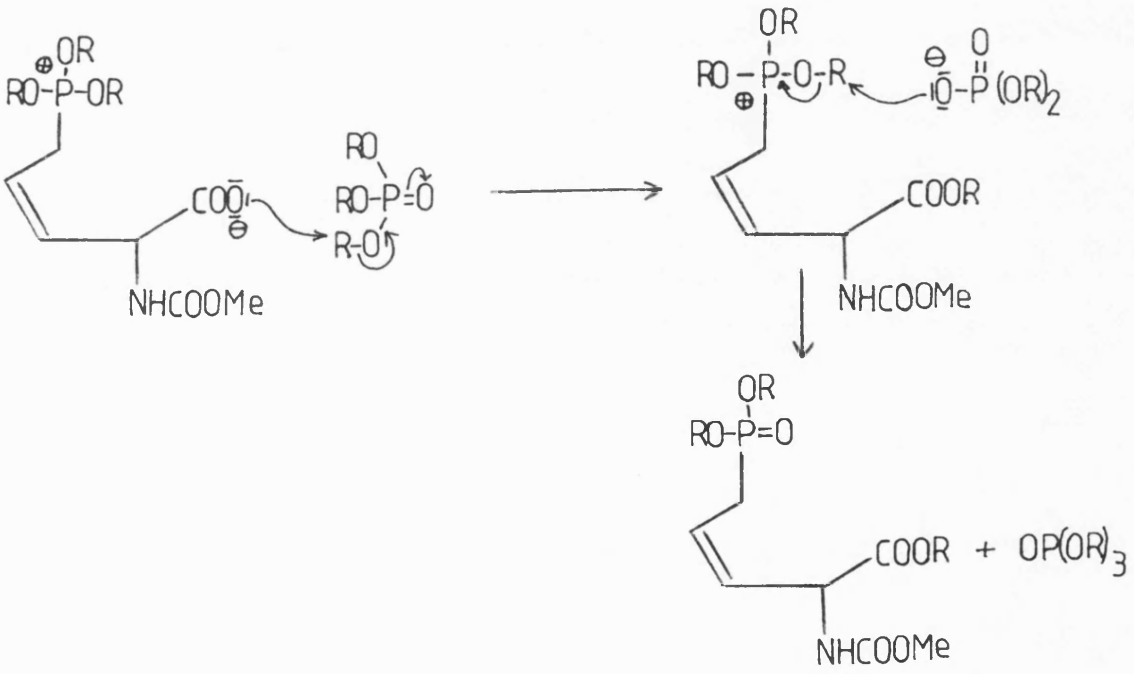


Figure 173

However, a trial reaction with trimethylphosphite containing trimethylphosphate was again complicated by competing side-reactions. Indeed phosphonate ring-opened material was only a minor product, the majority products seeming instead to be products from side-chain reaction, conjugated lactonic materials and N-methylated lactonic materials (by gc-ms analysis) (see Figure 174).

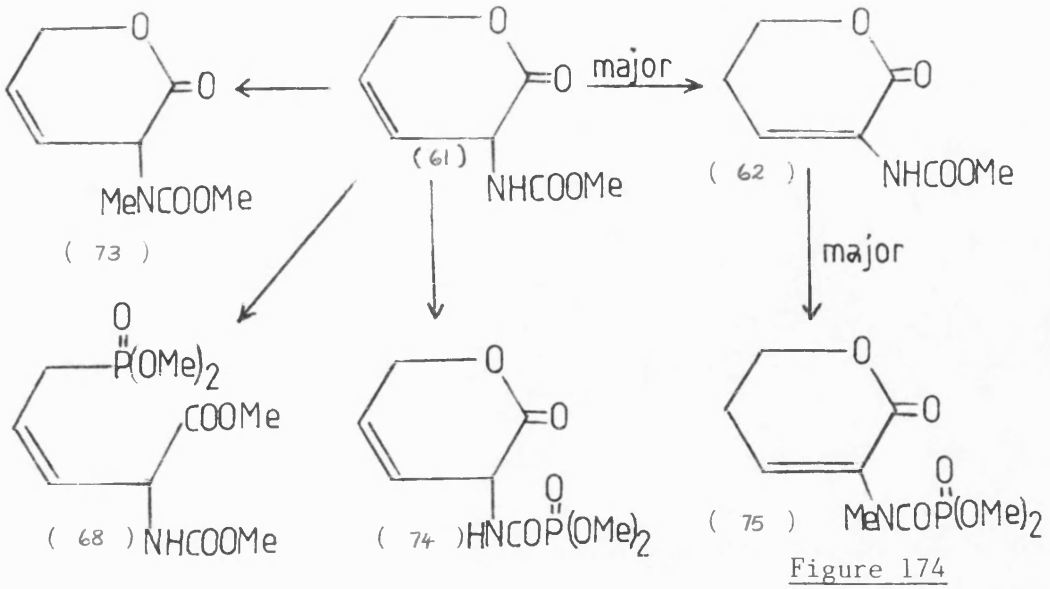


Figure 174

Similarly, the Arbusov reaction was known to be accelerated by the addition of halide salts of alkali metals.[166,186] (see Figure 175).

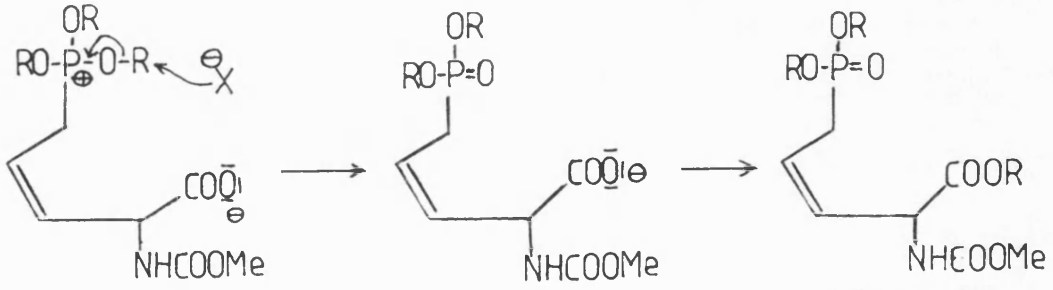


Figure 175

However addition of caesium fluoride (also known to aid the nucleophilicity of heteroatoms) caused no obvious improvement in the rate of reaction. Similarly, addition of lithium bromide showed no enhancement.

Attempts were made to catalyse the reaction by the addition of a protic or a Lewis acid (see Figure 176), but these were again complicated by competing side-reactions.

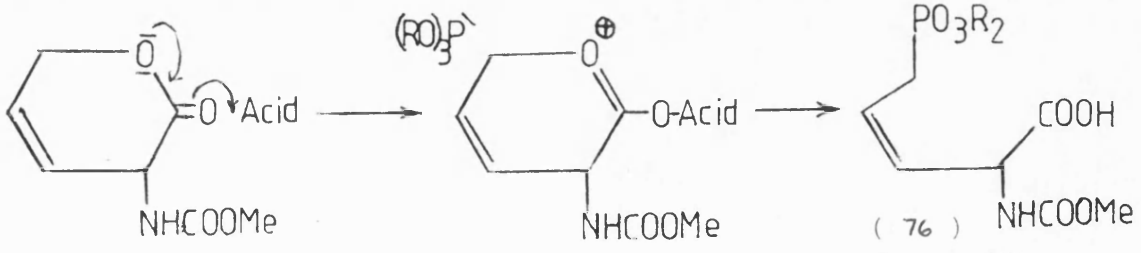


Figure 176

Attempted ring-opening of the lactone (61) with trimethylphosphite containing a catalytic quantity of H_2SO_4 at elevated temperature (90-100°C) was overwhelmed by methylation. The mixture, on gc-ms analysis, revealed the presence of products tentatively assigned the following structures (see Figure 177).

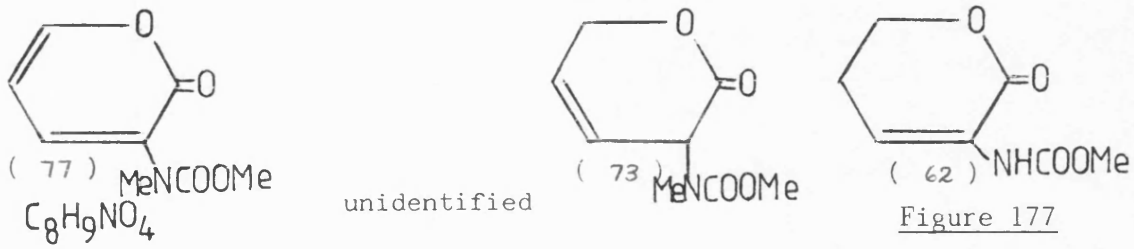


Figure 177

Similarly, conducting the ring-opening reaction in the presence of $SnCl_4$ was not successful. Products were recovered, but seemed to show evidence of conjugation and double bond saturation. Structures for these materials have not been elucidated.

Enhancement of the nucleophilicity of the phosphite reagent might be achieved by utilising the silyl β-effect. Silylating phosphites have been utilised for the production of phosphonates[189] and might be seen as convenient reagents in the lactone ring-opening reaction required. Again, the fundamental question of the regiochemistry of ring-cleavage (*O*-alkyl or *O*-acyl) becomes tantamount (see Figure 178).

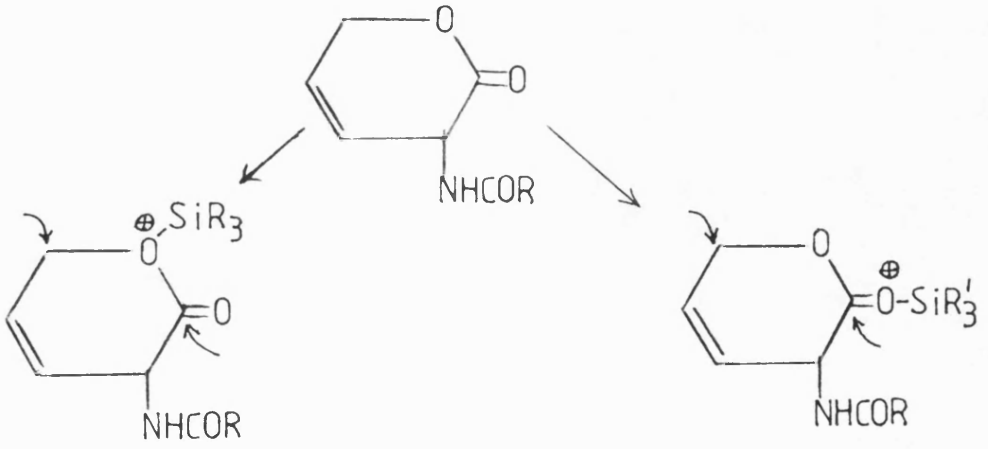


Figure 178

It is known that with a number of carbonyl-type materials (aldehydes, ketones, α,β-unsaturated aldehydes and ketones, esters, nitriles and acylphosphonates) silyl dialkylphosphite reagents undergo a ready acyl-phosphite insertion process[190] (see Figure 179).

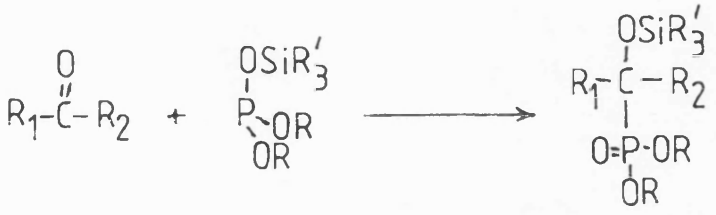
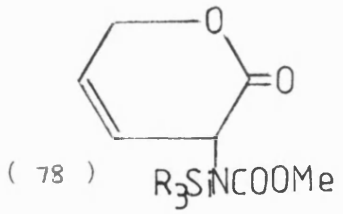
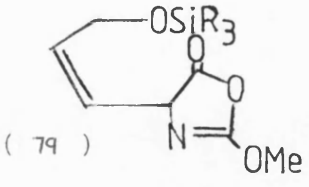


Figure 179

So it would appear that such phosphites would react with the substrate lactones to form acyl-phosphite products. Preformed silyl phosphites have not been studied here. However, using an *in situ* preparation of trimethylsilyldimethylphosphite [$HP(O)(OMe)_2$, NEt_3, TMSCl] to attempt a lactone ring opening was unsuccessful, the major product being the conjugated lactone. Minor side-products showed evidence of silylation, though not phosphorus incorporation, either on the side-chain or *via* sidechain participation (see Figure 180).



(78)



(79)

no sign of retro-dienic fragmentation in the mass spectra

Figure 180

The use of more basic reagent systems obviously have the worry that conjugation will be the major reaction. Also, previous studies on the reactions of sodium dialkylphosphites with lactones[125] gave

the products of *O*-acyl cleavage, rather than the desired *O*-alkyl cleavage (see Figure 181). Similarly the use of lithium diethyl methanephosphonate proceeded by *O*-acyl cleavage.[191]

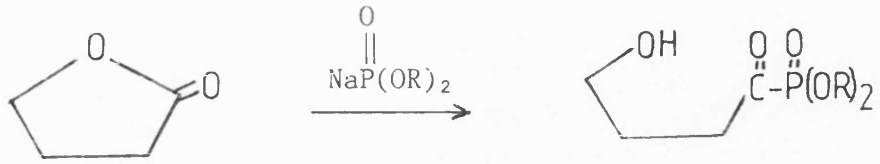


Figure 181

The reaction of the methylcarbamate protected amino-lactone (61) with sodium dimethylphosphite was examined, but the product has not proved to be identifiable, though phosphorus appeared to have been incorporated, probably as an acylphosphonate (see Figure 182).

	^{31}P nmr δ(ppm)
alkyl phosphonates[186]	27·8,
acyl phosphonates[187]	
R P(O)[C(O)NHPh]$_2$	23
R P(O)[C(O)NHC$_6$H$_4$NO$_2$]$_2$	15
products from reaction	8·4

Figure 182

However, the use of diethylphosphite to open butyrolactone[192] in the presence of the basic system of potassium fluoride adsorbed on alumina[193] has been reported to produce *O*-alkyl cleavage (see Figure 183).

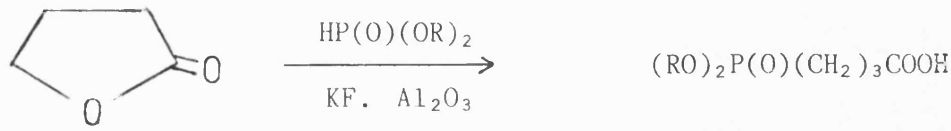
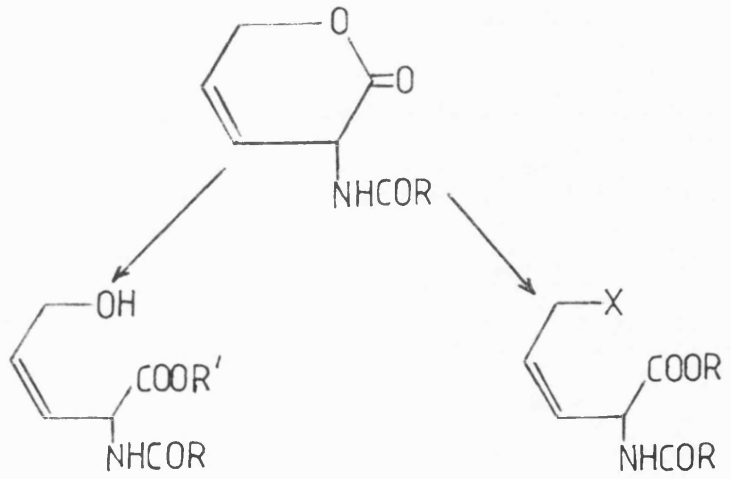


Figure 183

With our substrate lactones, however, conjugation of the lactone was evident.

Less direct approaches to the incorporation of the phosphonate ester functionality from the lactone substrates involve an initial ring-opening and an activation at the allylic position in such a way as to facilitate the nucleophilic substitution with a phosphorus species (see Figure 184).



followed by activation and displacement followed by displacement

Figure 184

First, the possibility of effecting the *O*-alkyl style cleavage[194] was explored. It was known that trialkylsilylhalides are able to cause ring-opening of lactones[195] in such a fashion (see Figure 185).

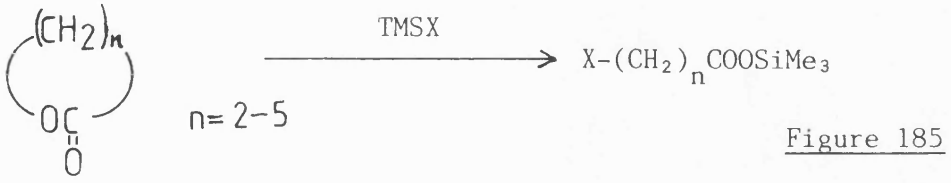


Figure 185

It was anticipated that a similar ring-opening of the lactonic substrates would allow access to useful alkylating reagents for reaction with phosphorus nucleophiles.

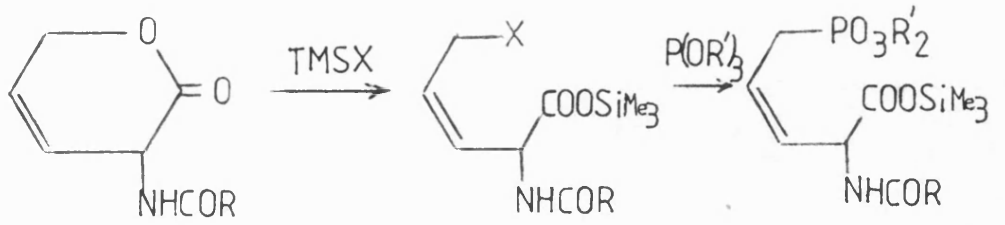


Figure 186

It had to be remembered, though, that trialkylsilylhalides are effective deprotection agents for a series of protecting groups[196] (among them carbamates, phosphonate esters and phosphite esters) so the choice of side-chain functionality was critical.

Treatment of the trichloroacetamide-protected lactone (49) with excess TMS-iodide (formed *in situ* from NaI/TMSCl in aceto-nitrile)[197] at elevated temperature was unsuccessful, however, in terms of isolation of the desired allylic iodide intermediate; it appeared instead that products recovered on work-up were starting material and some pyrone material (59) by gc-ms analysis (see Figure 187).

Figure 187

This recovery of starting material could of course be due to failure of the desired reaction; however, it might also be possible that hydrolysis of the intermediate silylated material, freeing the acid, could proceed with recyclisation onto the allylic iodide[198] (see Figure 188).

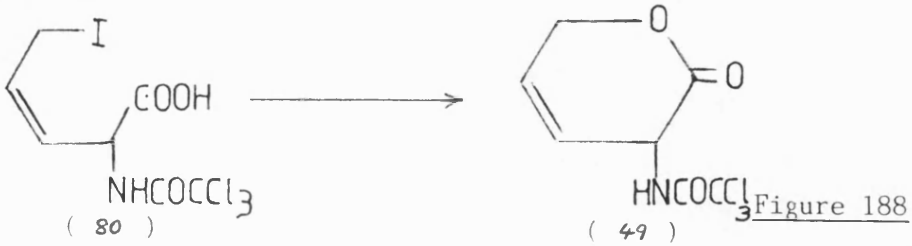


Figure 188

The pyrone product could have arisen by elimination of an intermediary allylic iodide, formed by allylic iodination (see Figure 189). This allylic iodination is possible since TMSI is known to disproportionate to hexamethyldisilane and iodine.*

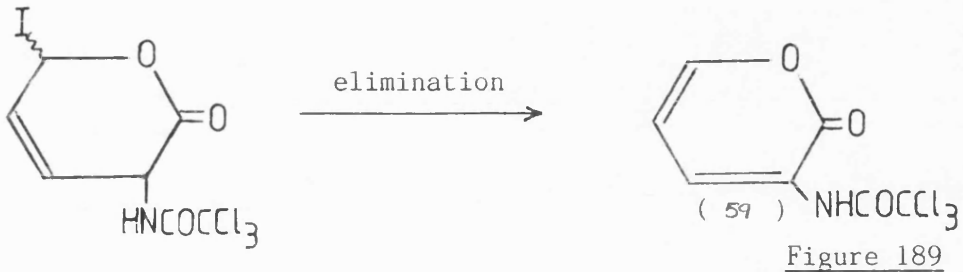


Figure 189

The precise mechanism of this elimination is not known, but participation of the sidechain must not be ruled out.

A similar *O*-alkyl cleavage had been reported by Meyers,[199] who utilised HBr in alcoholic solution to achieve the cleavage of an α- ethylenebutyrolactone (81) to an ω-bromoalkyl ester (see Figure 190).

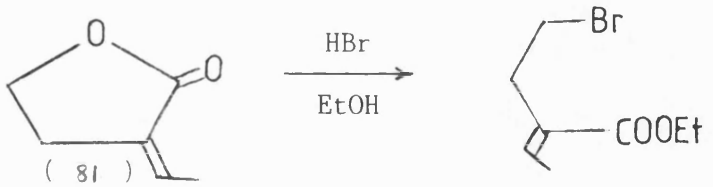
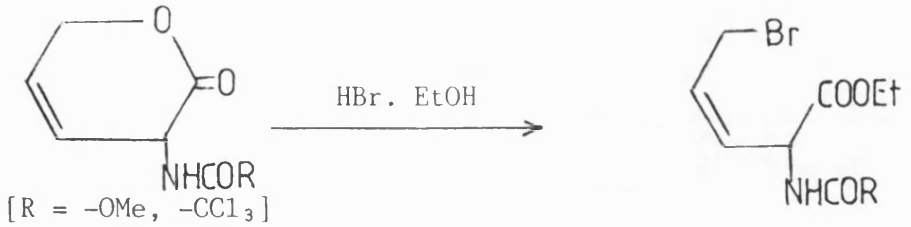


Figure 190

Interestingly, Meyers reported no addition to the conjugated double bond. Utilisation of this reagent system on the substrate lactones seemed to be an interesting possibility, but isolation of allylic bromides was only achieved in low yield (see Figure 191).

Footnote:

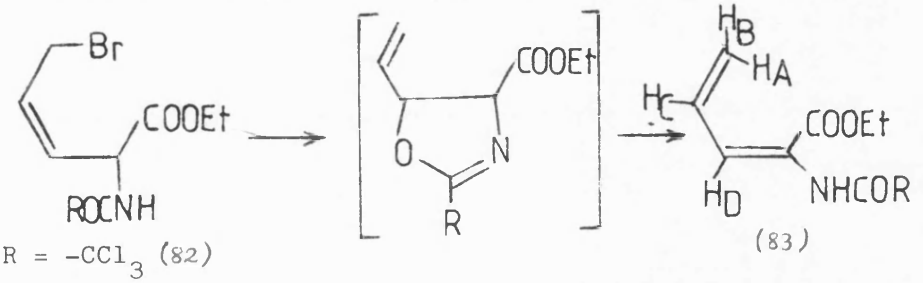
The reverse of this disproportionation is known as a convenient preparation of TMS iodide.[196]



[R = -OMe, $-CCl_3$]

Figure 191

Here the reaction was complicated by competitive eliminative processes, probably assisted internally by the nucleophilicity of the C-2 amide functionality, and conjugation (see Figure 192).



R = $-CCl_3$ (82) (83)

C_2H	5·4 ppm	H_A	5·65 ppm d of d of d
C_3H	5·25 ppm	H_B	5·53 ppm d of d of d
C_4H	6·1 ppm	H_C	7·4 ppm d of d of d
C_5H's	4·3, 4·1 ppm	H_D	7·88 ppm d

		m/z
mass spectra	[M+1]	366
	-HBr	286

J_{AB}	small
$J_{AC_{trans}}$	16·8 Hz
J_{BC}cis	10·1 Hz
J_{CD}	11·4 Hz

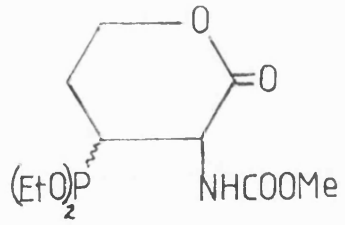
		m/z
mass spectra	[M+1]	286

Figure 192

Metal-catalysed ring-opening reactions were also considered. The unsaturated lactones could be seen as allylic acetates, which are well-known to undergo assisted cleavage *via* a metal π-allyl unit might perhaps be trapped at its terminus with a phosphorus species;[186,200] however decomplexation of the metal might not proceed with maintenance of the double geometry, giving rise to *cis-/trans-*

isomerisation.[186]

Reaction of the lactone (61) in triethylphosphite with $PdCl_2$ resulted not in lactone ring-opening, but rather in conjugation and a further product tentatively identified as the product of Michael addition to the conjugated lactone, by gc-ms analysis (see Figure 193).



(84) $C_{11}H_{20}NO_7P$ (309 amu)

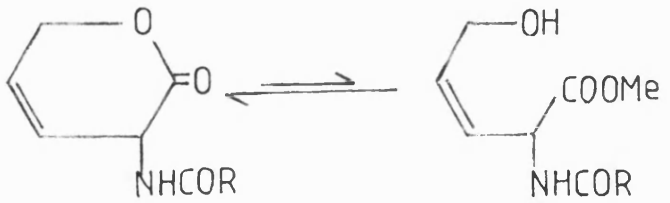
Fragments observed (m/z) 263 - EtOH

235 - NHCOOMe

Figure 193

Other attempts to open the lactone in more standard fashion, *via* a solvolytic cleavage, were also thwarted.

Acid-catalysed methanolysis did proceed, at room temperature, to a small extent giving the ring-opened hydroxymethyl ester; however an equilibrium was established and again the *cis*-double bond is responsible for constraining the conformation in such a way that the equilibrium position is biased well towards the lactone (see Figure 194).



[R = -OMe] (61) (85)

	m/z
$-H_2O$	185
-MeOH	153
-COOMe	144

Figure 194

When this reaction was performed at reflux other products were obtained, which remain unidentified, seeming to result from a dehydration process.

Similarly, failure was met when base-catalysed methanolysis was attempted. Here the obvious problem of conjugation again was dominant

and conjugated lactone produced, along with ring-opened materials which appeared both conjugated (both isomers) and unconjugated (see Figure 195).

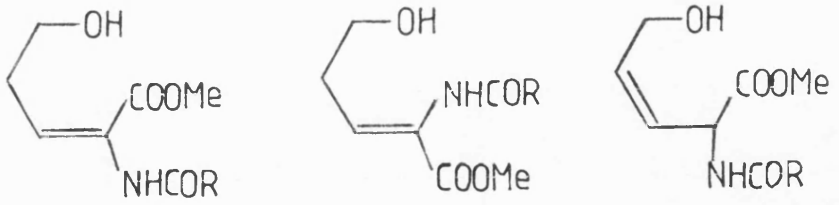


Figure 195

Attempts have also been made to force cleavage to predominate by an aminolytic type cleavage,[201] where the amine is a better nucleophile than the alcohol but a poorer leaving group (see Figure 196).

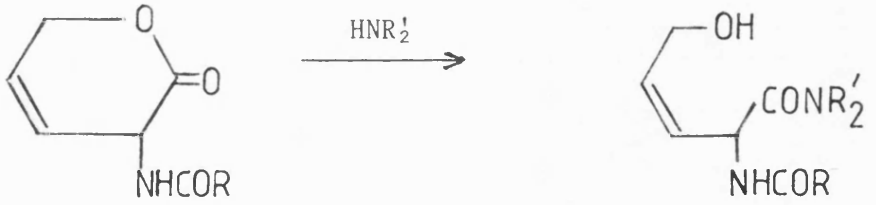
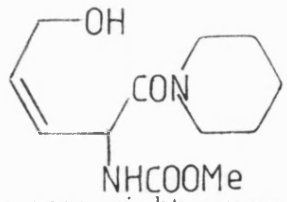


Figure 196

Trial-scale reactions have been examined with hydrazine,[202] dimethylamine[201] and piperidine.[203] There was some evidence for ring-opening proceeding under these conditions; specifically, there appeared to be partial formation of a chain product (86) with piperidine (at reflux in THF) by gc-ms analysis of the reaction, with evident competing conjugation (see Figure 197).



(86)

$C_{12}H_{20}N_2O_4$ (256 amu)

m/z 144 -COpiperidinyl

58 [$HOCH_2CH{=}CH_2$]

Further work in this area might prove fruitful.

Figure 197

Other means were also considered to allow access to suitable ring-opened materials.

The ability of a sugar lactol to undergo ring-chain tautomerism was explored with the desire of trapping the chain tautomer (see Figure 198).

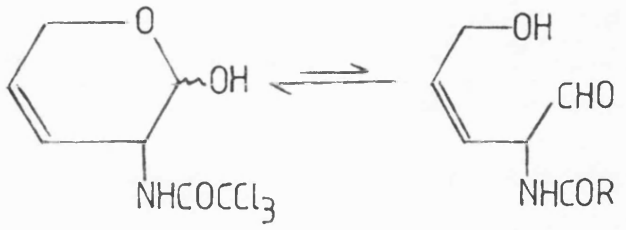


Figure 198

First, it was determined[204] to try and trap the ring-open form by utilising the greater nucleophilic reactivity of the primary allylic alcohol, compared to the secondary lactol, thus protecting this specifically from an equilibrium. However, acetylation (Ac_2O, pyr, DCM) proceeded only to give an anomeric acetate product mixture (87) (see Figure 199).

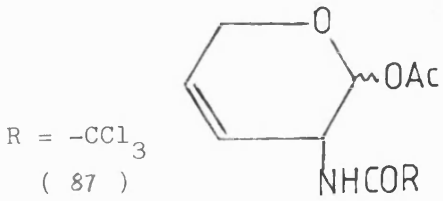


Figure 199

Then it was remembered that it would also be possible to capture the chain tautomer by aldehyde protection. This might be achieved by formation of an acetal (particularly a thioacetal) or perhaps a hydrazone.

Reaction of the lactol material with phenylhydrazine[205] appeared, however, to give only aminoglycoside type material (see Figure 200).

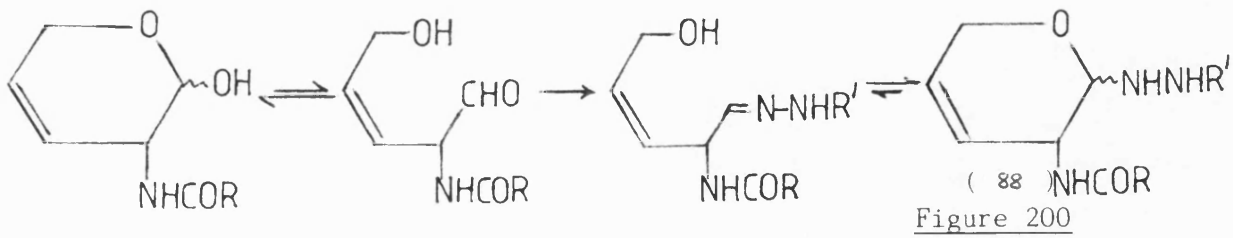
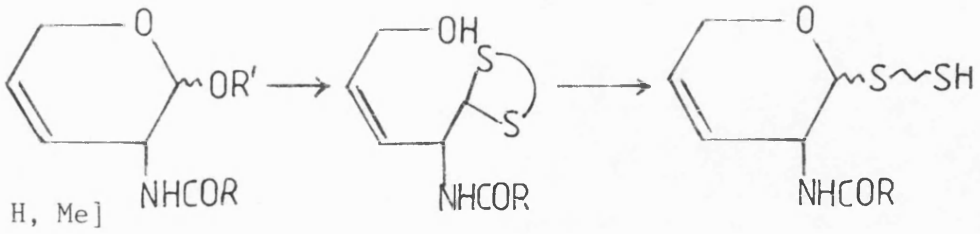


Figure 200

Similarly, all attempts to achieve dithioacetal formation[205,206] appear to have been unsuccessful, isolated products generally being oxacycles instead (see Figure 201).

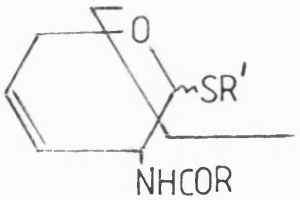


[R' = H, Me]

[R = CCl_3, OMe]

Figure 201

The structure of these products were determined by considering chemical and spectral evidence. Particularly the oxacycles gave a positive thiol test with 5,5'-dithiobis-(2 -nitrobenzoic acid). The infrared spectrum lacked an hydroxyl peak, the mass spectrum showed characteristic retro-dienic fragmentation (see Figure 202)



R' = Et, $-C_2H_4SH$

$-C_2H_6SH$

Figure 202

and of course consideration of the proton and ^{13}C nmr spectra showed evidence for the oxacycle structure (ie the asymmetry of the sulphur alkyl chain which would be lacking in the dithioacetal structure).

Interestingly, with propanedithiol, a second product was formed which gave a negative thiol test but analysis of the spectral data suggested that this was essentially a symmetrical 'dimeric' type material (see Figure 203).

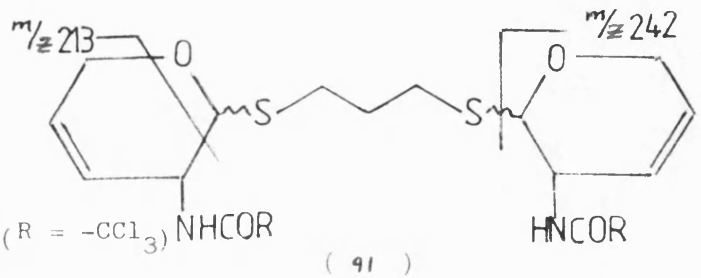


Figure 203

It had been suggested that these problems (conjugation, stability of ring-closed materials) might be alleviated by a protection of the double bond. However, no reasonable reaction sequence could be devised where both ready incorporation of the phosphonate ester and regeneration of the double bond with correct geometry and regiochemistry could be envisaged.

For instance, protection as a dibromide[207] would suffer from the phosphorus nucleophile preferentially reacting with the halide, and deprotection (Zn dust) would proceed with loss of double bond integrity. Conversely, methodology involving a Diels-Alder/retro Diels-Alder sequence[208] would possibly suffer from steric hindrance to nucleophile approach. Work in this area might be interesting.

Utilisation of the Novel Chiral Intermediates

Introduction

The unsaturated 2-amino glycosides and lactones reported here have obvious potential for further functionalisation, with a range of polyfunctionalised amino acids and amino sugars as obvious synthetic targets.

Essentially, such syntheses depend on the selective functionalisation and manipulation of the double bond in the intermediates. Epoxidation, for instance should allow access to a wide range of highly-functionalised structures.[209] Similarly, other products in theory approachable from such unsaturated intermediates include simple amino sugars (*via cis*-hydroxylation[210] or epoxidation), cyclopropyl amino acids (*via* cyclopropanation[211]) and novel chiral acyclic compounds with synthetic potential (*via* iodocyclisation[162]) as well as potential medicinal interest[212] (*via* ozonolysis) (see Figure 204).

Obviously, the merit of the intermediates in such processes depends upon there being high selectivity in the reactions. Here we report initial investigations into the reactivity of the intermediates.

Discussion

It would appear from initial studies that epoxidation of the double bond may be achieved with good face selectivity on glycosidic substrates, but that this selectivity seemed to be lost when lactonic substrates were studied. This observation might perhaps be explained in terms of the conformational control exerted by the stereoelectronic

NOTE - Italicised text refers to experimental work done by project students under the supervision of R.J.Ogilvie.

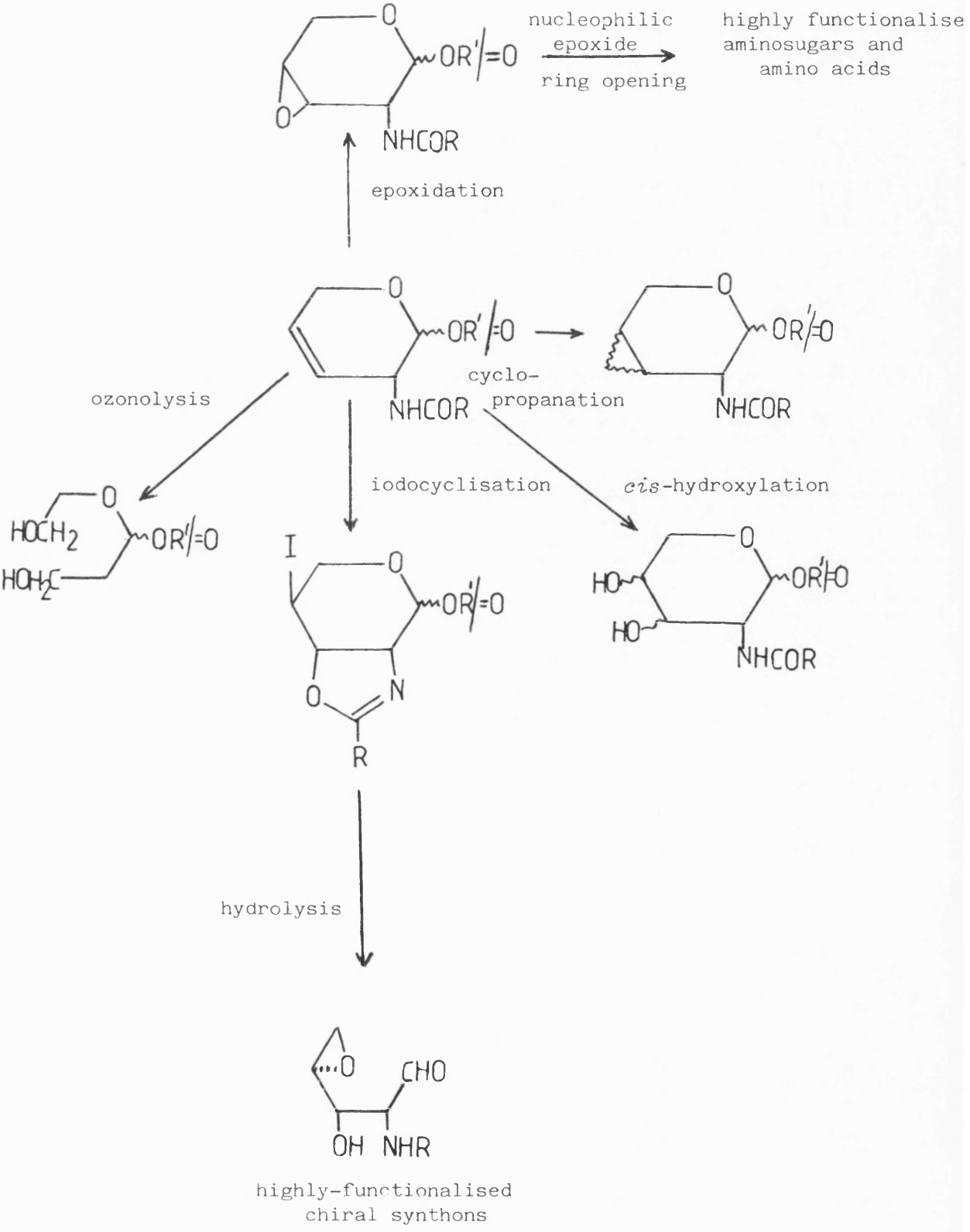

nucleophilic epoxide ring opening
highly functionalise aminosugars and amino acids
epoxidation
cyclo-propanation
ozonolysis
iodocyclisation
cis-hydroxylation
hydrolysis
highly-functionalised chiral synthons

Figure204

anomeric effect in the glycosides which is, of course, missing in the lactones. Thus, whereas the faces of the double bond in the conformationally-restricted glycosides are differentiated, in the lactones the two faces of the double bond are more equivalent.

Epoxidation of the glycosides (96) and (40b), for instance, proceeded quite cleanly (with mCPBA[213]) to give single epoxides[214] (on recrystallisation) whereas the lactone (61) seemed to give a mixture of epoxide stereoisomers.

The ^1H nmr spectrum of the epoxide (92) was difficult to interpret (see Appendix 3) ; particularly surprising was the magnetic equivalence of the C_5 methylene protons which appeared as a singlet at 3.98 ppm, suggesting that any coupling to C_4H was very small. This was further confirmed by the appearance of C_4H at 3.34 ppm, which was a doublet due to coupling to C_3H. Individual couplings were identified by a COSY-experiment (see Appendix 3) , which also suggested the presence of W-coupling between C_1H and both C_3H and one C_5H's, thus imparting useful data for analysis of ring conformation.

A lanthanide-induced shift study on the compound, using the shift reagent $Eu(fod)_3$, removed the magnetic equivalence of the protons on C_5H, though revealed no coupling to C_4H, and made possible a tentative assignment of the structure.

Lanthanide shift reagents complex with organic functional groups and induced shifts are observed, caused by the secondary magnetic field generated by the paramagnetic ion. At low concentrations of shift reagent to substrate a linear concentration dependence on the induced shift is observed, this shift corresponding to a first approximation[†],

† Footnote

Induced shift $\alpha \frac{3\cos^2\theta-1}{r^3}$

to the distance of the shifted proton from the paramagnetic ion.

The large induced shift of the NH proton might be explained by suggesting that the coordination occurred via *the amide. This group was known to be below the plane of the ring. The small induced shift experienced by the glycosidic methoxy-protons further suggested that the methoxy group was orientated well away from the site of complexation.*

If no assumptions were made concerning the epoxide geometry, there were a total of four possible chair conformations available to the epoxide (92) (see Figure 205) which are pairs of structures in equilibrium, with the equilibrium populations determined by normal conformational preferences and the stereoelectronic anomeric effect.

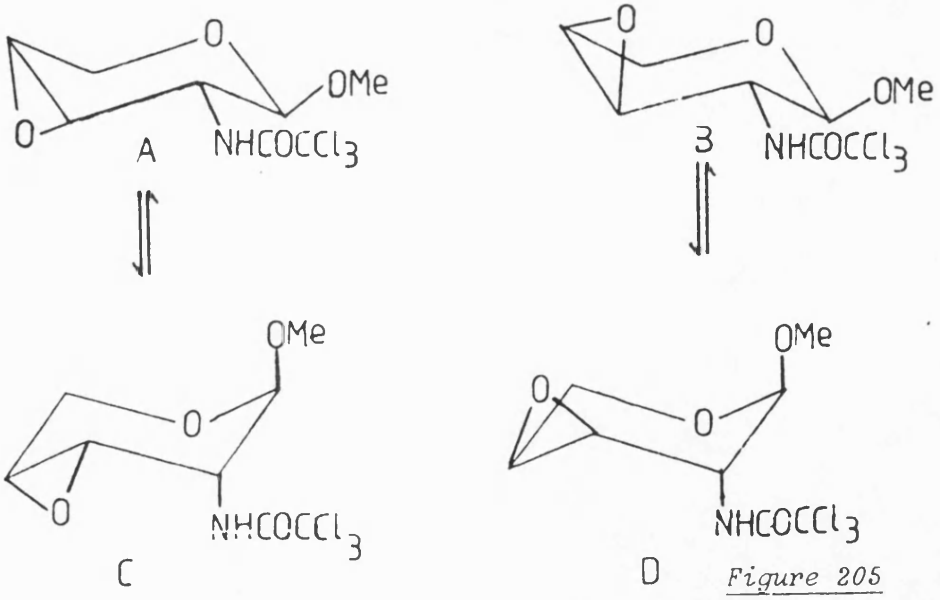


Figure 205

The occurrence of the C_5 protons as a singlet implied that the vicinal coupling to C_4H was small. Karplus analysis suggested a dihedral angle of approximately 60° for such a coupling, though the

application of the Karplus equation to carbohydrate systems is known to be of dubious merit. However belief in this analysis allowed the elimination of conformations A and D, which, from analysis of models, have dihedral angles of 100° and 20° respectively. Similarly, consideration of models of B and C and examination of the two for the required W-couplings suggested that C was the most likely structure. This is interesting since the absence of stereoelectronic anomeric stabilisation in B also mitigates against that conformation. Also, C presents a complete chelating unit for complexation to the lanthanide shift reagent (see Figure 206), accounting for the induced shifts observed.

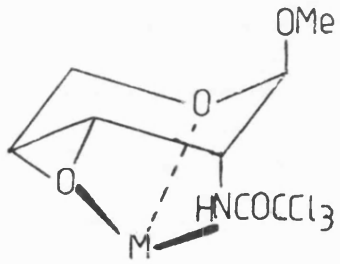


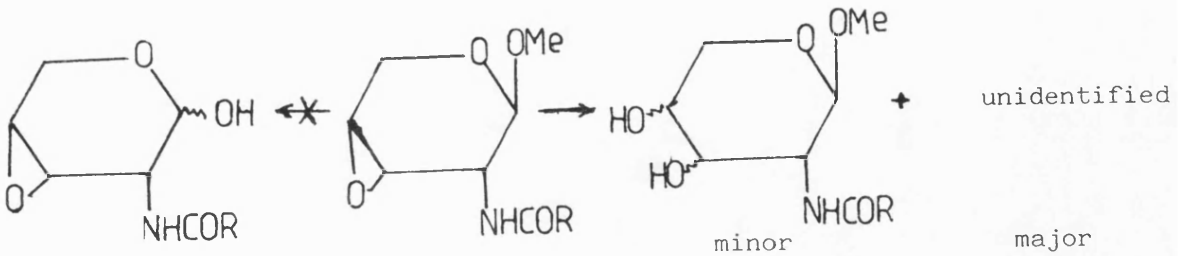
Figure 206

Obviously, this is a simplified interpretation, ignoring any angular dependence in the induced shift, any possible conformational change caused by complexation to the lanthanide and relying overmuch on Karplus analysis. An X-ray crystal structure is awaited to confirm (or refute) this interpretation.

This conformation, C, may have been formed by reagent approach control of the peracid by complexation to the amide. Interestingly, none of the other structures could be envisaged as having such a selective mode of formation.

Further functionalisation of such epoxides might also be possible by *trans*-diaxial ring opening with a range of nucleophiles. Again, the value of such processes is to some extent determined by the degree of regioselection achieved in the reactions. Interestingly, initial investigation suggested that the glycosidyl epoxide was ring-opened (NaN_3,DMF; 39%) with essentially complete regiocontrol to give a single azide product. The position of nucleophile incorporation has not yet been identified, and speculation on the basis of required *trans*-diaxial ring-opening is complicated since the conformations A and C are in equilibrium and reaction might have occurred in either, with a reversal of the position of nucleophile incorporation.

It was investigated whether it was possible to convert the glycosidyl epoxides to the corresponding lactone epoxides (by hydrolysis and oxidation) giving lactones containing epoxides of clean stereochemistry. However initial studies of acid hydrolysis suggested that epoxide cleavage predominated (see Figure 207) .



R = $-CCl_3$ (92) (94)

R = - OMe (93) (95)

Figure 207

Utilisation of the unsaturation in the substrates to form *cis*-diols[210] has also been studied (OsO_4 in THF) but here the lactone (61) gave a more selective reaction than did the glycoside (9b), where a mixture of products was obtained (these might not just be diastereomeric diols, a ^1H nmr peak at 8.2 ppm perhaps being indicative of over-oxidation) . The stereochemistry of the product *cis*-diol from (61) has not yet been elucidated.

Further studies into the utility of the novel intermediates in synthesis would be merited; time only allowed preliminary studies to be undertaken here.

Experimental

D-Xylose (Sigma grade) was obtained from the Aldrich Chemical Company. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1310 spectrophotometer. ^{1}H nmr spectra were recorded at 60 MHz on an Hitachi-Perkin Elmer R-24B, at 100 MHz on a JEOL JNM-PS-10, at 270 MHz on a JEOL JNM-GX 270 and at 400 MHz on a JEOL JNM-GX-400. Unless otherwise stated, ^{1}H nmr spectra refer to data recorded at 270 MHz in $CDCl_3$, chemical shifts recorded with respect to internal tetramethylsilane. ^{31}P nmr spectra were recorded at 161.8 MHz (chemical shift with respect to external H_3PO_4) and ^{13}C nmr spectra at 67.8 MHz (chemical shift with respect to internal tetramethylsilane) again in $CDCl_3$ unless otherwise stated. UV spectra were recorded using a Perkin-Elmer Lambda 3 spectrophotometer in ethanol solution. Mass spectra were obtained with a VG Analytical 7070 E mass spectrometer and 2035 data system (electron ionisation at 70 eV and chemical ionisation achieved with isobutane). GC-MS spectra were recorded with electron ionisation.

Reactions were monitored either by thin layer chromatography on Merck-DC-Alufolien Kieselgel 60 F 254 using an appropriate eluant (1:1 ethyl acetate : petrol), or by capillary gas chromatography on an A_i 93 gas chromatograph (standard run conditions: 100-280°C, 15°C per minute; 25 m OV-1 capillary column, 0.25 mm i.d.).

Column chromatographic purification was effected using pressurised short path columns (through Amicon 35-70 60A silica), or, more commonly, employing the suction driven method on a sinter funnel (through Merck 7736 Type 60 H silica). Generally, eluants would consist of ethyl acetate/petrol mixtures.

Product visualisation was effected after tlc by the following sequence:

a) Ultraviolet irradiation of the plates impregnated with a fluorescent indicator,

b) Exposure to iodine vapour,

c) Development using a 10% ethanolic solution of H_2SO_4. This reagent was found to be extremely useful since it gave a different colour reaction with a 3,4-unsaturated material (gold) than with 1,2- or 2,3-unsaturated materials (purple).

Optical rotations of materials were obtained on standard solutions in de-ethanolated $CHCl_3$ (by passage through activated basic alumina) at about 24°C and 598 nm (the sodium D-line) using a Perkin-Elmer 141 polarimeter.

Elemental analyses were performed either by the Butterfield service or in house (A. Carver) on a Carlo Erba Strumentazione 1106.

Solvents

Petrol refers to the petroleum ether fraction of boiling point 60-80°C (redistilled) and ether refers to diethyl ether. Solvents used for chromatography were re-distilled and reaction solvents generally dried by appropriate procedures, and distilled.

Note: Peaks assigned in the mass spectra to halide-containing compounds have the correct isotopic distribution^{150} - only the base peak of a series is quoted in the text.

2,3,4-tri-O-acetyl-D-xylopyranosyl bromide (1)[216]

Acetic anhydride (4 ml, 0.042 mol) was placed in a three-necked flask (100 ml) equipped with overhead mechanical stirring, $CaCl_2$ drying tube and a thermometer. A small portion of D-xylose was added with continuous stirring, followed by dropwise addition of a catalytic quantity of perchloric acid (72%, 2 drops). This addition caused a slight yellowing of the solution.* Anhydrous D-xylose (1.0 g, 6.6 mmol) was added in small portions, allowing the solution to clear before addition of the next portion. This process should be conducted at such a rate as to maintain flask temperature at about 40°C. (The solution so formed was stable overnight if required). Fifteen minutes after complete addition of D-xylose, the solution was cooled to about 15°C in a cooled bath and then dry red phosphorus (0.32 g, 10 mmol) was added. (No red phosphorus must remain on the walls of the flasks or it will react with bromine with burning). After several minutes, dropwise addition of bromine (1.8 g, 0.58 ml, 11.25 mmol) was begun in such a way that the temperature of the reaction was maintained between 15°C and 20°C. This was best achieved by continual cooling in an ice-bath, especially when working on a larger scale (50 g or more). Ten minutes after complete bromine addition distilled water (0.42 ml, 23 mmol) was added dropwise, keeping the temperature below 20°C. (This addition proceeds very exothermally so cooling and stirring must be very efficient, even with a slow addition rate). When all the water had been added the reaction mixture was allowed to stand

* It is important when scaling-up this process to reduce the amount of perchloric acid added as too much causes severe discolouration of the solution, which should retain a golden hue.

for ninety minutes and then diluted with chloroform (5 ml). Unreacted phosphorus was allowed to settle and the mixture filtered through Celite, washing the residue with further chloroform. The filtrate was placed in a separating funnel (100 ml) which had been three-quarters filled with crushed ice. The mixture was thoroughly mixed, the chloroform layer separated and the aqueous layer quickly extracted with a little chloroform (5 ml). The combined chloroform extracts were washed as quickly as possible, three times with portions of iced water (10 ml each), iced sodium bicarbonate solution (3 x 10 ml each) and finally with three further portions of iced-water. The yellow chloroform solution was then dried over $CaCl_2$, the solution becoming clear after slight warming. After addition of a little activated charcoal dust and about twenty minutes standing, the mixture was filtered under vacuum through Celite. The filtrate was evaporated under reduced pressure (bath temperature $<45°C$). Usually during concentration a slurry of crystals was obtained - if not, a little dry ether was added and then the bromide crystallised out with scratching. For several further reactions these crystals were used without further purification. Further purification could be effected by recrystallisation from warm dry ether. Crystallisation quickly occurred while standing at 20°C and was increased by evaporation under reduced pressure. When the solution was filled with yellow crystals the mixture was placed in the refrigerator and stored overnight. Then filtration under vacuum yielded a yellow crystalline solid which was washed with cold (-20°C) dry ether to provide colourless crystals (0.753 g; 33%). This material was

highly unstable but could be stored under dry nitrogen in a refrigerator.

3,4-di-O-acetyl-D-xylal (2)[216]

Acetic acid (50% in distilled water, 7.5 ml) in a small round-bottomed flask was cooled with an ice-salt mixture (or a CO_2-cooled bath) and zinc copper couple added (1.5 g, 23 mmol). This mixture was stirred vigorously and the solid tri-O-acetyl-D-xylopyranosyl bromide (0.75 g, 2.2 mmol) was added in small portions over a period of two hours, then stirred for an additional hour. (During all these operations, the temperature of the reaction should not exceed -10°C). After the reaction period, the excess zinc was filtered off and the resulting filtrate diluted with iced-water (5 ml). This solution was then extracted with several portions of chloroform (two volumes in total) and the combined chloroform solution then washed with two or three volumes of water, two volumes of chilled sodium bicarbonate solution, then again with two volumes of water. The chloroform solution was then dried ($MgSO_4$) and evaporated under reduced pressure (bath temperature not greater than 20°C). The remaining oil was then purified by elution through silica (1:9 ethyl acetate : petrol). The fraction of Rf 0.75 (1:1 ethyl acetate : petrol) yielded the 3,4-di-O-acetyl-D-xylal (2) (0.2 g; 46%), m.p. 34-35°C (lit. 40°C)[216] $[\alpha]_D^{29}$ ($CHCl_3$) -333° (c 59.7 mg in 10 ml); (Found: C, 53.9; H, 6.2. Calc. for $C_9H_{12}O_5$: C, 54.0; H, 6.0); ν_{max} ($CHCl_3$) 1740 (ester) and 1600 cm^{-1} alkene); δ_H (100 MHz, $CDCl_3$) 6.45 (1H, d, J 5Hz, 1-H), 4.88 (3H, br, 2-H, 3-H

and 4-H), 4.00 (2H, m, 5α-H and 5β-H) and 2.00 (6H, s, two-$CO\underline{CH}_3$); δ_c ($CDCl_3$) 169.8, 169.7 (each, C=O), 148.1 (1-C), 97.5 (2-C), 67.3 (CH), 63.7 (5-C), 63.5 (CH) and 21.1, 20.9 (each, -$CO\underline{CH}_3$); m/z (C.I.) 140 (M-CH_3COOH).

It should be noted that other more polar fractions yielded a major reaction by-product (Rf 0.25) as a solid (0.75 g) which was not further purified, but which was tentatively assigned as 2,3,4-tri-O-acetyl-D-xylose 93) ν_{max} ($CHCl_3$) 3580 (-OH) and 1750 (ester); δ_c ($CDCl_3$) 170.5, 170.3 (each, C=O, 1 coincident), 90.2 (1-C), 71.5, 69.4, 69.2 (2-C, 3-C and 4-C), 58.3 (5-C), and 20.7 (3 x $CO\underline{CH}_3$).

This zinc reduction could also be adapted to progress to the xylal species without isolation of the bromide, and such a process has been used on scales of up to 200 g of starting xylose.

Preparation of 3,4-di-O-acetyl-D-xylal (2) by zinc reduction of a crude solution of the bromide (1)

After stirring the bromination for ninety minutes at room temperature, the reaction mixture was filtered (without dilution by chloroform) and the residue washed with glacial acetic acid. This solution was then added dropwise to a chilled solution of sodium acetate trihydrate (1 g) in aqueous acetic acid (5 ml acetic acid, 3 ml distilled water) containing the zinc-copper couple dust (2 g) and the mixture stirred for three hours, when the product was isolated as before. The best overall yield of the xylal (2) achieved without isolation of the bromide was 27%.

Activation of zinc

i) Zinc could be activated by stirring dust (10 g) and 10% aqueous hydrochloric acid (4 ml) for 2-3 minutes, then filtering and washing with water and acetone, under suction.

ii) Zinc-Copper Couple

Analar zinc dust (50 g) was stirred with 3% aqueous hydrochloric acid (20 ml) for a few minutes, decanting the acid, and washing sequentially with three volumes of 3% HCl (aq), five volumes of distilled H_2O, two volumes of $CuSO_4$ (aq) (5 g $CuSO_4$ in total), five volumes of distilled water, four volumes of absolute ethanol and five volumes of absolute ether. The zinc was filtered under vacuum, dried and stored in a desiccator over KOH.

Other activation steps were taken, including I_2, I^- and catalytic platinum ions but were found to bring about no improvement.

Other methods were tried to improve the yield of 3,4-di-O-acetyl-D-xylal (2) from bromide (1); none of these attempts were successful. These comprised a) a reduction with sodium naphthalenide; b) a reduction *via* the Grignard reagent; c) a reduction with zinc in AcOH/THF or AcOH/DCM and d) a reduction with zinc in TFA.

Preparation of ethyl 4-O-acetyl-2,3-dideoxy-D-glycero-pent-2-enopyranosides (4)[135]

To a solution of 3,4-di-O-acetyl-D-xylal (2) (0.18 g, 0.9 mmol) in dry ethanol (2 ml) was added a catalytic quantity of freshly-

distilled (CaH_2) BF_3 etherate (0.04 ml, 0.03 mmol). The resulting mixture was stirred for forty minutes at about 30-40°C before deactivating the catalyst by slow addition of anhydrous sodium carbonate (0.12 g). TLC analysis (1:1 ether-petrol) revealed formation of two major products. Filtration and evaporation *in vacuo* gave a mixture which was most effectively separated by radial chromatography (eluant: 1:1 ether : petrol) and afforded ethyl 4-*O*-acetyl-2,3-dideoxy-α-D-*glycero*-pent-2-enopyranoside (4a) (31.3 mg, 18.7%).

ν_{max} ($CHCl_3$) 1700 cm^{-1} (ester); δ_H (400 MHz, $CDCl_3$) 5.93 (1H, m, 3-H), 5.85 (1H, ddd, *J* 10.3, 2.3, 1.7 Hz, 2-H), 5.27 (1H, m, 4-H), 4.94 (1H, dd, *J* 2.3, 1.2 Hz, 1-H), 3.85 (3H, m, 1'-H, 5α-H, 5β-H), 3.54 (1H, dt, *J* 9.5, 7.1 Hz, 1'-H), 2.06 (3H, s, $-CO\underline{CH_3}$) and 1.23 (3H, t, *J* 7.1 Hz, $CH_2\underline{CH_3}$); δ_C ($CDCl_3$) 170.4 (C=O), 129.5, 128.7 (each, =CH), 94.2 (1-C), 65.1 (4-C), 64.1 (CH_2), 60.2 (CH_2), 20.1 ($-CO\underline{CH_3}$) and 15.3 ($-CH_2\underline{CH_3}$); m/z (EI) 156 (M - CH_2O) and 141 (M - OEt), and the more polar ethyl 4-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enopyranoside (4b) (85.2 mg; 50.9%) δ_H (400 MHz, $CDCl_3$) 6.06 (1H, ddd, *J*, 10.1, 4.5, 1.1 Hz, 3-H), 6.02 (1H, dd, *J* 10.1, 2.6 Hz, 2-H), 5.00 (1H, d, *J* 2.6 Hz, 1-H), 4.94 (1H, m, 4-H), 4.16 (1H, dd, *J* 13.0, 2.9 Hz, 5-H), 3.82 (1H, dq, *J* 9.7, 7.1 Hz, 1'-H), 3.81 (1H, m, 5-H), 3.54 (1H, dq, *J* 9.6, 7.1 Hz, 1'-H), 2.07 (3H, s, $-CO\underline{CH_3}$) and 1.23 (3H, t, *J* 7.1 Hz, $-CH_2\underline{CH_3}$); δ_C ($CHCl_3$) 170.5 (C=O), 131.1 (2-C), 125.0 (3-C), 92.9 (1-C), 63.9 (CH_2), 63.5 (4-C), 61.3 (5-C), 21.1 ($-CO\underline{CH_3}$) and 15.3 ($-CH_2\underline{CH_3}$); m/z (C.I.) 187 (M+1), 156 (M-CH_2O), 141 ([M+1]-HOEt), 127 ([M+1]-HOAc) and 81 (pyryllium cation).

These were identical to the materials reported by Fraser-Reid[135] The corresponding methyl glycosides (5) were similarly prepared in 52% yield but these were not separated as the two acetates; rather, they were deprotected to the alcohols (7) prior to separation.

Improved preparation of methyl 4-O-acetyl-2,3-dideoxy-D-glycero-pent-2-enopyranosides (5)[136]

To a solution of the xylal (2) (1.0 g, 5 mmol) in dry dichloromethane (20 ml) containing methanol (0.425 ml, 10.5 mmol) was added a catalytic quantity of $SnCl_4$ (0.03 ml, 0.25 mmol) and the mixture stored at room temperature for ca. 8 hours. GC-analysis then indicated complete conversion to the glycosides (5). The products were recovered by pouring the reaction mixture into saturated aqueous $NaHCO_3$ (1 volume) and extracting the mixture with three portions of dichloromethane. The combined extracts were washed with brine and dried ($MgSO_4$) before evaporation under reduced pressure yielded a residue which was purified by chromatography (eluant: ethyl acetate - petrol) to give a yellow oil containing the acetates (5) (0.78 g, 91%) which were identical with those obtained from the rearrangement of (2) with BF_3 etherate.

Palladium-assisted rearrangement of the 3,4-di-O-acetyl-D-xylal (2)[140]

To a solution of the 3,4-di-O-acetyl-D-xylal (2) (1.51 g, 7.56 mmol) in dry methanol (10 ml) over crushed 4A° molecular

sieves under argon was added $PdCl_2$ (0.67 g, 3.78 mmol) and the mixture stirred for three hours when gc-analysis showed formation of both anomers (5a and 5b) in this reaction.

Methyl 2,3-dideoxy- D-glycero-pent-2-enopyranosides (7) [217]

A solution of the allylic acetates (5) (26.54 g, 0.153 mmol) in methanol (300 ml) was stirred for one hour over catalytic K_2CO_3 at room temperature to effect complete deprotection. Evaporation in vacuo and filtration through silica gel (in ethyl acetate) gave the alcohols (7) as an anomeric mixture (13.4 g, 69%). Chromatography (eluant: 1:1 ethyl acetate : petrol) did not effect complete separation of the anomers but gave a range of fractions. Early fractions contained methyl 2,3-dideoxy-α-D-glycero-penta-2-enopyranoside (7a)[217];$[\alpha]_D$ ($CHCl_3$) 127.4° (c. 58 mg in 10 ml); δ_H (400 MHz, $CDCl_3$) 6.04 (1H, ddt, J 10, 2, 1.5 Hz, 3-H), 5.78 (1H, m, 2-H), 4.82 (1H, m, 1-H), 4.21 (1H, m, 4-H), 3.8 (1H, ddd, J 11, 7, 1 Hz, 5-H), 3.67 (1H, dd, J 11, 8 Hz, 5-H), 3.42 (3H, s, -OMe) and 2.1 (1H, b, -OH); δ_C ($CDCl_3$) 133.2 (=CH), 127.5 (=CH), 95.6 (1-C), 63.7 (5-C), 63.0 (4-C), and 55.8 (-OMe). This was followed by fractions containing the anomeric mixture and then fractions containing methyl 2,3-dideoxy-β-D-glycero-pent-2-enopyranoside (7b); $[\alpha]_D$ ($CHCl_3$) 91.9° (c 95.6 mg in 10 ml); δ_H (400 MHz, $CDCl_3$) 6.15 (1H, dd, J 10, 7, 1 Hz, 3-H), 5.90 (1H, ddd, J 10, 3, 0.7 Hz, 2-H), 4.85 (1H, dd, J 3, 1 Hz, 1-H), 4.1 (1H, dd, J 13, 3 Hz, 5-H), 3.8 (1H, dd, J 13, 2 Hz, 5-H), 3.8 (1H, m, 4-H), 3.43 (3H, s, -OMe), and 2.12 (1H, br, -OH); δ_C ($CDCl_3$) 129.2 (=CH), 128.4 (=CH), 94.3 (1-C), 64.2 (5-C), 61.5 (4-C) and 55.7 (-OMe); m/z

(E.I.) 100, (M-CH_2O), (C.I.) 113 ([M+1] -H_2O), 99 ([M+1] -MeOH).

Ethyl 2,3-dideoxy-D-glycero-pent-2-enopyranosides (6)

The previously separated ethyl glycosides (4a and 4b) were similarly deprotected to the allylic alcohols (6a), (6b) previously characterised by Fraser-Reid[138]. The data recorded for these alcohols are in accord with those reported previously.

Ethyl 2,3-dideoxy-α-D-glycero-pent-2-enopyranoside (6a); δ_H (400 MHz, $CDCl_3$) 6.0 (1H, ddt, J 10.2, 2.5, 1.1 Hz, 3-H), 5.74 (1H, ddt, J 10.25, 2.4, 1.75 Hz, 2-H; simplified on deuteration to dt through loss of 1.75 Hz coupling to -OH), 4.90 (1H, dtd, J 2.4, 1.4, 0.56 Hz, 1-H; simplified on deuteration to dt through loss of 0.56 Hz coupling to -OH), 4.19 (1H, m, 4-H), 3.82 (1H, dq, J 9.6, 7.1 Hz, 1'-H), 3.76 (1H, ddd, J 11.0, 5.3, 1.0 Hz, 5-H), 3.67 (1H, ddt, J 11.0, 8.0, 0.5 Hz, 5-H), 3.52 (1H, dq, J 9.6, 7.1 Hz, 1'-H), 2.27 (1H, br d, J 8.6 Hz, -OH, exch.) and 1.21 (3H, t, J 7.1 Hz, -$OCH_2\underline{CH_3}$) δ_C ($CDCl_3$) 133.4 (=CH), 127.3 (=CH), 94.2 (1-C), 64.1 (CH_2) 63.4 (CH_2), 62.7 (4-C) and 15.3 (-$OCH_2\underline{CH_3}$); m/z (E.I.) 114 (M-CH_2O), 99 (M-OEt), (C.I.) 127 ([M+1]-H_2O).

Ethyl 2,3-dideoxy-β-D-glycero-pent-2-enopyranoside (6b); δ_H (400 MHz, $CDCl_3$) 6.09 (1H, ddt, J 10.0, 4.7, 1.1 Hz, 3-H), 5.86 (1H, ddd, J 10.0, 3.1 0.5 Hz, 2-H), 4.92 (1H, dd, J 3.1, 1.15 Hz, 1-H), 4.10 (1H, ddd, J 12.2, 2.6, 0.5 Hz, 5-H), 3.81 (1H, dq, J 9.6, 7.15 Hz, 1'-H), 3.75 (1H, m, 4-H), 3.75 (1H, dt, J 12.2, 1.4 Hz, 5-H), 3.52 (1H, dq, Jq 9.6, 7.1 Hz, 1'-H), 2.28 (1H, brd, J 9.44 Hz, -OH, exch.) and 1.21 (3H, t, J 7.1 Hz, -$OCH_2\underline{CH_3}$). δ_C ($CDCl_3$) 129.3 (=CH), 128.5 (=CH), 93.1 (1-C), 64.4 (CH_2), 63.8 (CH_2), 61.3 (4-C)

and 15.2 ($-OCH_2\underline{CH}_3$); m/z (E.I.) 114 ($M-CH_2O$), 99 (M-OEt), (C.I.) 127 ($[M+1]-H_2O$).

Methyl 2,3-dideoxy-4-O-(2',2',2'-trichloroacetimidoyl)-D-glycero-pent-2-enopyranosides 98)

Hot, oven-dried glassware was charged with sodium hydride (0.04 g, 1.6 mmol) and the vessel blown cold with dry N_2. To this flask was added sodium-dried diethyl ether (25 ml). To this stirred ethereal suspension was added a solution of the alcohol (7b) (2.12 g, 16.3 mmol) in dry ether (25 ml) over aperiod of five minutes from a syringe. After the evolution of hydrogen had ceased the reaction mixture was stirred for a further fifteen minutes before cooling in an ice-salt bath. Trichloroacetonitrile (1.84 ml, 18 mmol) in dry ether (5 ml) was then added over a period of fifteen minutes and the mixture allowed to stir for 1-2 hours at this temperature until the reaction was complete as judged by tlc. The reaction mixture was then allowed to warm to room temperature before concentrating the light amber solution under reduced pressure. A solution of methanol (0.06 ml, 1.6 mmol) in hexane (100 ml) was then added and the mixture shaken vigorously for a few minutes and re-evaporated in vacuo. (Addition of too much alcohol may reverse the reaction). The remaining solid was pre-adsorbed onto silica gel and purified by column chromatography to give a colourless solid. Recrystallisation from ethyl acetate afforded **methyl 2,3-dideoxy-4-O-(2',2',2'-trichloroacetimidoyl)-β-D-glycero-pent-2-enopyranoside** (8b) (4.2 g, 94%); m.p. 56°C; $[\alpha]_D$ ($CHCl_3$) 101.85° (c. 43.3 mg in 5 ml); (Found: C, 35.1, H, 3.9; N, 5.2.

$C_8H_{10}NO_3Cl_3$ requires C, 35.0; H, 3.7; N, 5.1); ν_{max} ($CHCl_3$) 3350 (N-H) and 1660 cm^{-1} (C=NH); δ_H ($CDCl_3$) 8.25 (1H, br, NH), 6.22 (1H, m, 3-H), 6.10 (1H, m, 2-H), 5.10 (1H, m, 4-H), 4.94 (1H, dd, J 3.0, 0.8 Hz, 1-H), 4.20 (1H, dd, J 13.1, 2.8 Hz, 5-H), 4.00 (1H, dt, J 13.2, 1.2 Hz, 5-H) and 3.45 (3H, s, -OMe); δ_C ($CDCl_3$) 162.1 (C=N), 131.4, 124.1 (each, =CH), 94.1 (1-C), 91.3 ($-CCl_3$ weak) 67.7 (5-C), 60.5 (4-C) and 55.6 (-OMe); ms (E.I.) 243 ($M-CH_2O$), 113 ($M-OCNHCCl_3$), (C.I.) 274, [M+1].

Similarly **methyl 2,3-dideoxy-4-O-(2',2',2'-trichloroacetimidoyl)-α-D-glycero-pent- 2-enopyranoside** (8a) was obtained from (7a) as colourless crystals, m.p. 44-45°C (on recrystallisation from ethyl acetate) in 76% yield. δ_H ($CDCl_3$) 8.1 (1H, b, NH), 5.9 (1H, dd, J 10, 2 Hz, =CH), 5.7 (1H, dd, J 10, 1 Hz, =CH), 5.3 (1H, m, 4-H), 4.75 (1H, s, 1-H), 3.9-3.8 (2H, m, 5α-H and 5β-H) and 3.37 (1H, s, -OMe).

The reaction was also performed on the anomeric mixture (7) and the anomeric imidates (8) obtained as a mixture in 92% yield.

Methyl 2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent- 3-enopyranosides (9)

The trichloroacetimidate (8b) (8.1 g, 2.9 mmol) was dissolved in sodium-dried xylene (100 ml) and treated at reflux under a $CaCl_2$-guard tube until complete conversion was noted by gc-analysis (> 18 hours). [TLC analysis of this reaction was misleading due to the difference in intensity of response to H_2SO_4/MeOH observed for the reactant (purple) and the product (gold)]. The cooled solution was then passed through a silica column eluting initially with

toluene and subsequently with dichloromethane to give **methyl 2,3,4-trideoxy-2-(2',2',2'-trichloroacetimido)-β-D-glycero-pent-3-enopyranoside** (9b) as a yellow solid (7.2 g, 90%) which was recrystallised from ethyl acetate/petrol to afford colourless crystals, m.p. 91°C; $[\alpha]_D$ = -216.1° (c. 62.8 mg in 5 ml); (Found: C, 35.0; H, 3.6; N, 5.1. $C_8H_{10}NO_3Cl_3$ requires C, 35.0; H, 3.7; N, 5.1); ν_{max} ($CDCl_3$) 3400 (NH) and 1710 cm^{-1} (amide C=O); δ_H ($CDCl_3$) 6.9 (1H, brd, NH), 6.08 (1H, m, =CH), 5.82 (1H, m, =CH), 4.71 (1H, s, 1-H), 4.29-4.07 (3H, m, 2-H, 5α-H and 5β-H) and 3.50 (3H, s, -OMe); δ_C ($CDCl_3$) 161.4 (C=O), 131.0, 120.0 (each, =CH), 98.9 (1-C), 92.3 (CCl_3), 58.9 (5-C), 56.1 (2-C) and 47.1 (-OMe); m/z (E.I.) 213, (M-HCOOMe), (C.I.) 274 ([M+1]) and 242 ([M+1]-MeOH).

Attempting to thermally rearrange the α-anomeric imidate (8a) was unsuccessful due to the extended reaction time required (> 1 week) and considerable losses due to charring. However the anomeric mixture was rearranged in several days at xylene reflux temperature (60% recrystallised yield).

Methyl 4-O-benzoyl-2,3-dideoxy-α-L-glycero-pent-2-enopyranoside (10)

To a solution of the alcohol (7a) (0.64 g, 4.9 mmol) in THF (25 ml) under a nitrogen atmosphere were added, successively, triphenylphosphine (2.56 g, 9.8 mmol), benzoic acid (1.19 g, 9.8 mmol) and diethylazodicarboxylate (1.54 ml, 9.8 mmol) all dissolved in a little THF and the mixture stirred at room temperature for one hour. The solvent was then removed by evaporation under reduced pressure, the residues redissolved in DCM (25 ml) and washed with

$NaHCO_3$ (aq), then H_2O before drying the organic solution ($MgSO_4$). Filtration, evaporation and purification by column chromatography (1:19 ethyl acetate in petrol) gave the benzoate (10) (1.0 g, 87%) which could be recrystallised as colourless crystals from ethyl acetate-petrol, m.p. 46-48°C; $[\alpha]_D$ ($CHCl_3$)-172° (c. 35.9 mg in 5 ml); ν_{max} ($CHCl_3$) 1710 cm^{-1} (C=O); δ_H (100 MHz, $CDCl_3$) 8.0-7.5 (5H, m, aromatic CH's), 6.1 (2H, m, 2-H and 3-H), 5.1 (1H, m, 4-H), 4.95 (1H, d, J 2 Hz, 1-H), 4.0 (2H, m, 5α-H and 5β-H) and 3.5 (3H, s, -OMe); δ_C ($CDCl_3$) 166.1 (C=O), 133.1, 130.9, 129.7, 128.3, 125.1 (aromatic and =CH), 94.2 (1-C), 63.8 (4-C), 61.3 (5-C) and 55.6 (-OMe).

Methyl 2,3-dideoxy-α-L-glycero-pent-2-enopyranoside (11)

A solution of the benzoate (10) (0.70 g, 3.0 mmol) in dry methanol (10 ml) containing NaOH (0.1 g) was stirred for one hour at room temperature. The product was recovered by evaporation in vacuo, re-solution of the residues in brine and extraction with three portions of ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to give the alcohol (11) (0.265 g, 65%) as an oil $[\alpha]_D$ ($CHCl_3$)-100.4° (c. 35.9 mg in 5 ml); δ_H (60 MHz, $CDCl_3$) - superimposable with that of the enantiomeric material (7b) - 6.15 (1H, dd, J 9, 4 Hz, 3-H), 5.90 (1H, dd, J 9, 3 Hz, 2-H), 4.85 (1H, d, J 3 Hz, 1-H), 4.15 (1H, dd, J 12, 3 Hz, 5-H), 3.85 (2H, m, 5-H and 4-H), 3.45 (3H, s, -OMe) and 2.85 (1H, b, -OH).

Methyl 2,3-dideoxy-4-O-(2',2',2'-trichloroacetimidoyl-α-L-glycero-pent-2-enopyranoside (12) - A Preliminary Investigation

The reaction was performed as previously described but the imidate recovered proved difficult to recrystallise, m.p. 49-50°C (crude); $[\alpha]_D$ ($CHCl_3$) -86.5°.

Methyl 2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranosides (13) - A Preliminary Investigation

The reaction was performed as previously described and the amide recovered was recrystallised from ethyl acetate-petrol, m.p. 74-75°C; $[\alpha]_D$ ($CHCl_3$) 221°. (c. 80.1 mg in 5 ml), ν_{max} (CH_2Cl_2) 3400 (NH) and 1720 cm^{-1} (amide C=O); δ_H (60 MHz, $CDCl_3$) 6.9 (1H, b, NH), 6.0 (2H, m, 3-H and 4-H), 4.7 (1H, s, 1-H), 4.2 (3H, m, 2-H, 5α-H and 5β-H) and 3.5 (3H, s, -OMe); m/z (E.I.) 213 (M-HCOOMe), 178 (M-Cl), 96 ([213]-CCl_3); (C.I.) 274 (M+1) and 242 ([M+1]-MeOH).

Attempted formation of ethyl 2,3-dideoxy-4-O-toluenesulphonyl-D-glycero-pent-2-enopyranosides (14)

Tosyl chloride (0.46 g, 2.4 mmol) was added to a chilled solution (in an ice-bath) of the alcohol (6) (0.23 g, 1.6 mmol) in dry pyridine (5 ml) and the resulting solution allowed to react for two days whilst being maintained at low temperature (< 0°C). TLC analysis then showed partial formation of a mobile product, presumed to be the tosylate (14). Extended reaction time (and the addition of a catalytic quantity of dimethylaminopyridine) produced eventually a predominance on tlc analysis of a material still less polar than the presumed tosylate, but also revealed that starting

material still remained. This mobile material produced *via* the presumed tosylate intermediate appeared to be a mixture of chlorine- substituted materials by gc-ms analysis, which were not pursued further. m/z: 132 (M-CH_2O), 127 (M-Cl) and 117 (M-OEt) for the major isomer (15); 127 (M-Cl), 117 (M-OEt) and 88 (M-HCOOEt) for the minor isomer (16). Both anomers of the alcohol (6a and 6b) gave similar results.

Attempted formation of ethyl 2,3-dideoxy-4-*O*-trifluoromethyl-sulphonyl-D-*glycero*-pent-2-enopyranosides (17)

Addition of triflic anhydride (0.2 ml, 1.2 mmol) to a solution of the allylic alcohol (6), (0.16 g, 1.1 mmol) equilibrated in an ice-salt bath in DCM (10 ml) containing pyridine (0.18 ml, 2.2 mmol) caused the solution to yellow considerably. TLC analysis revealed complete loss of starting material, washing the organic solution with portions of aqueous 2M HNO_3, aqueous $CuSO_4$, aqueous saturated $NaHCO_3$ and H_2O before drying ($MgSO_4$), allowed the recovery of aldehyde (19) as a golden oil (33.6 mg, 24%) which rapidly decolourised. δ_H (100 MHz) 9.5 (1H, d, *J* 8 Hz, CHO), 7.2-6 (4H, m, =CH), 3.8 (2H, m, $-O\underline{CH_2}CH_3$) and 1.3 (3H, t, *J* 6-7 Hz, $-OCH_2\underline{CH_3}$).

Lewis acid catalysed reaction of the alcohol (6) with potassium thiocyanate

To a stirred solution of the allylic alcohol (6) (0.172 g, 1.2 mmol) and potassium thiocyanate (0.23 g, 2.4 mmol) in dry acetonitrile (5 ml) was added, dropwise, over a period of five

minutes, a solution of $BF_3.Et_2O$ (0.29 ml, 2.4 mmol) in acetonitrile (2 ml). After 15 minutes at room temperature, tlc analysis revealed loss of starting material and formation of a mixture of products. The reaction mixture was diluted with dichloromethane (50 ml), washed with ice water (two volumes), aqueous $NaHCO_3$ (1 volume) and saturated brine (1 volume), dried (Na_2SO_4) and evaporated in vacuo. Analysis of the crude mixture revealed incorporation of an isothiocyanate (ir ν_{max} ($CHCl_3$) 2050 cm^{-1}) but loss of the ethyl glycoside fragment (by nmr).

Methyl 2,3-deoxy-4-O-methanesulphonyl-D-glycero-pent-2-enopyranosides (20)

To a solution of the alcohol (7a) (0.46 g, 3.56 mmol) in dry dichlormethane (25 ml) cooled in an ice-bath was added pyridine (0.86 ml, 10.7 mmol), followed by dropwise addition of distilled methanesulphonylchloride (0.41 ml, 5.34 mmol). The reaction flask was wrapped in foil and stored in the refrigerator for four days when the analysis showed complete conversion to a more mobile material. The reaction mixture was diluted with dichloromethane (to 50 ml), washed with chilled 2 M HCl (2 x 1 volume), chilled $CuSO_4$ (aq) (2 x 1 volume), chilled saturated $NaHCO_3$ (aq) (2 x 1 volume) chilled distilled water (2 x 1 volume) and dried ($MgSO_4$). Evaporation in vacuo gave a golden-brown oil which contained a methanesulphonyl contaminant (nmr), removed by chromatography (eluant - $CHCl_3$) to give **methyl 2,3-deoxy-4-O-methanesulphonyl-α-D-glycero-pent-2-enopyranoside** (20a) as yellow crystals (0.62 g, 84%), m.p. 43-44°C, ν_{max} (CH_2Cl_2) 1350 (SO_2) and 950 cm^{-1} (SO);

δ_H (60 MHz, $CDCl_3$) 5.95 (2H, s, 2-H and 3-H), 5.15 (1H, t, J 6.7 Hz, 4-H), 4.80 (1H, d, J 2 Hz, 1-H), 3.90 (2H, d, J 6.7 Hz, 5α-H and 5β-H), 3.40 (3H, s, -OMe) and 3.05 (3H, s, $-OSO_2Me$); δ_C ($CDCl_3$) 132.2, 123.7 (each, =CH), 93.6 (1-C), 69.1 (4-C), 61.1 (5-C), 55.8 (-OMe) and 38.8 ($-OSO_2Me$).

In a similar fashion, **methyl 2,3-deoxy-4-O-methanesulphonyl--D-glycero-pent-2-enopyranoside** (20b) was recovered as colourless crystalline material (73%), m.p. 65-66°C, δ_H (60 MHz, $CDCl_3$) 6.15 (2H, m, 2-H and 3-H), 4.90 (2H, m, 1-H and 4-H), 4.10 (2H, m, 5α-H and 5β-H), 3.45 (3H, s, -OMe) and 3.05 (3H, s, $-OSO_2Me$).

Methyl 2,3,4-trideoxy-4-thiocyanato-L-glycero-pent-2-enopyranosides (21)

To a solution of the mesylate (20b) (420 mg, 2.0 mmol) in acetonitrile (10 ml) was added potassium thiocyanate (0.235 g, 2.42 mmol) and the mixture stirred at room temperature for 6 days, when tlc showed complete conversion of the starting material to a more mobile product. This was recovered by evaporation of the acetonitrile and re-solution in dichloromethane, pre-adsorption onto silica gel and chromatography (eluant: ethyl acetate-petrol) giving **methyl 2,3,4-trideoxy-4-thiocyanate-α-L-glycero-pent-2-enopyranoside** (21a) (278 mg, 80%) as an oil, $[\alpha]_D$ ($CHCl_3$) -166.4°C (c 58.3 mg in 10 ml); (Found: C, 49.5; H, 5.35; N, 8.2. $C_7H_9NO_2S$ requires C, 49.1; H, 5.3; N, 8.2); ν_{max} ($CHCl_3$) 2150 cm^{-1} (SCN); δ_H ($CDCl_3$) 5.99 (2H, s, 2-H and 3-H), 4.88 (1H, s, 1-H), 4.05-3.9 (3H, m, 5α-H, 5β-H and 4-H) and 3.45 (3H, s, -OMe); δ_C ($CDCl_3$) 131.1, 127.3 (each, =CH), 109.7 (SCN), 94.5 (1-C), 61.7 (5-C), 55.9 (-OMe)

and 41.1 (4-C); m/z: (E.I.) 140 (M-OMe), 113 (M-SCN), 110 ([140] $-CH_2O$), (C.I.) 172 ([M+1]), 140 ([M+1]-MeOH) and 113 ([M+1]-HSCN).

In the same way, **methyl 2,3,4-trideoxy-4-thiocyanato-β-L-glycero-pent-2-enopyranoside** (21b) was recovered after four days at room temperature in 52% yield. ν_{max} (CH_2Cl_2) 2160 cm^{-1} (SCN); δ_H (400 MHz, $CDCl_3$) 6.1-6.05 (2H, m, 2-H and 3-H), 4.91 (1H, d, J 1.5 Hz, 1-H), 4.3 (1H, dd, J 12.7, 2.6 Hz, 5-H), 4.0 (1H, m, 5-H), 3.75 (1H, m, 4-H) and 3.45 (3H, s, -OMe); δ_C ($CDCl_3$) 131.1, 125.1 (each, =CH), 94.0 (1-C), 61.8 (5-C), 55.9 (-OMe) and 42.5 (4-C); m/z (E.I.) 141 ($M-CH_2O$), 140 (M-MeO), 113 (M-SCN) (C.I.) 172 ([M+1]), 140 ([M+1]-MeOH) and 113 ([M+1]-HSCN).

Methyl 2,3,4-trideoxy-2-isothiocyanato-L-glycero-pent-3-enopyranosides (22)

A solution of the thiocyanate (21a) (105 mg, 0.61 mmol) in toluene (5 ml) was heated under reflux ($CaCl_2$-guard tube) for ca. 4 hours until tlc analysis revealed consumption of starting material. Products were recovered simply by evaporation of the solvent and purification of the residues by chromatography (eluant: 1:4 ethyl acetate-petrol) affording **methyl 2,3,4-trideoxy-2-isothiocyanato-α-L-glycero-pent-3-enopyranoside** (22a) as an oil (85.4 mg, 81.6%), $[\alpha]_D$ ($CHCl_3$) 155.3° (c 36.9 mg in 10 ml), (Found: C, 49.1; H, 5.3; N, 8.1. $C_7H_9NO_2S$ requires C, 49.1; H, 5.3; N, 8.2) ν_{max} (CH_2Cl_2) 2040 cm^{-1} (NCS); δ_H ($CDCl_3$) 5.92 (1H, m, =CH), 5.70 (1H, dd, J 10.3, 2.3 Hz, =CH), 4.87 (1H, d, J 3.3 Hz, 1-H), 4.34 (1H, m, 2-H), 4.4-4.0 (2H, two m, 5α-H and 5β-H) and 3.56 (3H, s, -OMe); δ_C ($CDCl_3$)(128.3, 120.8 (each, =CH), 96.6 (1-C), 60.5 (5-C), 56.2

(2-C) and 53.1 (-OMe); m/z: (E.I.) 140 (M-MeO), 111 (M-HCOOMe), (C.I.) 172 ([M+1]), 140 ([M+1]-MeOH) and 113 ([M+1]-HNCS).

Similarly, **methyl 2,3,4-trideoxy-2-isothiocyanato-β-L-glycero-pent-3-enopyranoside** (22b) was recovered in 68.6% yield, ν_{max} ($CHCl_3$) 2050 cm^{-1} (NCS); δ_H ($CDCl_3$) 6.00 (1H, m, =CH), 5.76 (1H, m, =CH), 4.68 (1H, d, J 3.3 Hz, 1-H), 4.22 (2H, m, 5α-H and 5β-H), 4.02 (1H, m, 2-H) and 3.51 (3H, s, -OMe); m/z (E.I.) 139 (M-MeOH) and 111 (M-HCOOMe).

Methyl 2-acetamido-2,3,4-trideoxy-L-glycero-pent-3-enopyranosides (23)

A solution of the isothiocyanate (22) (30.4 mg, 0.18 mmol) in acetic anhydride (2 ml) containing catalytic sodium acetate (15 mg) was heated under reflux ($CaCl_2$ guard tube) for 7 days. When the reaction appeared complete by tlc, the solvent was evaporated as an azeotrope with toluene and the residue purified by column chromatography (eluant: ethyl acetate - petrol) affording the **acetamide** (23) (18.4 mg, 60.5%), ν_{max} (CH_2Cl_2) 3420 (NH) and 1655 cm^{-1} (C=O); δ_H ($CDCl_3$) 5.9-5.8 (2H, m, =CH and NH), 5.6-5.5 (1H, m, =CH), 5.30 (1H, s, 1-H), 4.75 (1H, m, 2-H), 4.15 (1H, m, 5-H), 4.07 (1H, m, 5-H), 3.49 (3H, s, -OMe) and 2.01 (3H, s, $-COCH_3$); m/z: (E.I.) 111 (M-HCOOMe, found 111.0683 C_6H_9NO requires 111.0665), (C.I.) 172 ([M+1]), 140 ([M+1]-MeOH) and 111 (M-HCOOMe).

Attempted oxidative rearrangement of 3,4-di-O-acetyl-D-xylal (2) to the α,β-unsaturated lactone (29)

To a solution of 3,4-di-O-acetyl-D-xylal (2) (0.23 g, 1.1

mmoles) in dry dichloromethane (5 ml) equilibrated in an ice-salt bath was added m-chloroperbenzoic acid (0.21 g, 1.2 mmol), then BF_3. etherate (0.15 ml, 1.1 mmol). The clear reaction mixture was removed from the coolant and allowed to stir for 15-20 minutes before tlc analysis. During this period the reaction mixture darkened considerably (pale yellow → pink → black) . The reaction mixture was then poured into a saturated solution of $NaHCO_3$ (1 volume) containing sodium thiosulphate (5-10 mg). This treatment removed most of the dark colouration from the solution, giving a golden-yellow dichloromethane solution which was diluted with DCM (20 ml) and washed with H_2O (2 x 1 volume) and saturated brine (1 volume) and dried ($MgSO_4$). TLC indicated a complex mixture of products and no desired product (29) was identifiable, but nmr analysis of the crude material revealed signs of aldehydic materials.

4-O-Acetyl-2,3-dideoxy-D-glycero-pent-2-enopyranoses (26)

To a suspension of the glycoside (5) (0.45 g, 2.6 mmol) in distilled water (15 ml) was added a little Amerlyst 15 H^+ resin and the mixture left to stir at room temperature until tlc analysis revealed complete consumption of starting material (ca. 48 hrs). The resin was then filtered off, the aqueous solution saturated with NaCl and extracted exhaustively with ethyl acetate. Chromatography (eluant: ethyl acetate-petrol) afforded the anomeric lactol mixture (26) (0.17 g, 42.2%) as colourless crystals, m.p. 66-67°C, ν_{max} ($CHCl_3$) 3570 (OH), 3370 (OH-H bound) and 1715 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.10 (1H, d, J 2 Hz, =CH), 5.97 (1H, m, =CH),

5.43 (0.75 H, d, J 5 Hz, 1-H), 5.33 (0.25 H, d, J 6.5 Hz, 1-H), 5.21 (0.25 H, m, 4-H), 4.98 (0.75 H, m, 4-H), 4.28 (1H, dd, J 13, 2.5 Hz, 5-H), 3.90 (1H, m, 5-H), 3.24 (0.25 H, d, J 6.7 Hz, -OH), 3.05 (0.75 H, d, J 5 Hz, -OH) and 2.10 (3H, s, -OMe); δ_C ($CDCl_3$) 170.7 (C=O), 131.4, 128.3 (2, minor), 125.1 (each, =CH), 89.4 m, 87.6 (each, 1-C), 64.6 m, 63.1 (each, 4-C), 61.4 m, 61.3 (each, 5-C), 21.1 (-CO$\underline{C}H_3$); m/z: (E.I.) 128 (M-CH_2O), 98 (M-HOAc), (C.I.) 159 ([M+1]), 141 ([M+1]-H_2O). Also recovered was a mixture of more polar aldehydes (0.09 g, 22.9%) which were partially separated on further chromatography to give one of the aldehydes, **(4S)-5-O-acetyl-4,5-dihydroxy-pent-2-enal (28)** in a pure form, m.p. 61-62°C, δ_H ($CDCl_3$) 9.60 (1H, d, J 7.7 Hz, CHO), 6.83 (1H, dd, J 15.7, 4 Hz, 3-H), 6.43 (1H, m, 2-H), 4.71 (1H, m, 4-H), 4.28 (1H, dd, J 11.5, 4.5 Hz, 5-H), 4.16 (1H, dd, J 11.5, 6 Hz, 5-H) 3.2 (1H, br, OH) and 2.1 (3H, s, -$COCH_3$). δ_C ($CDCl_3$) 193.3 (CHO), 171.3 (C=O ester), 153.8, 132.5 (each, =CH), 69.4 (4-C), 66.7 (5-C) and 20.8 (OCO$\underline{C}H_3$); m/z: (E.I.) 98 (M-AcOH), (C.I.) 159 ([M+1]) and 141 ([M+1]-H_2O).

(4S)-4-O-Acetyl-4,5-dihydroxy-pent-2-enoic acid, δ-lactone (29)

To a solution of the 2,3-unsaturated lactol (26) (0.147 g, 0.93 mmol) dissolved in dry dichloromethane (10 ml) buffered with sodium acetate was added pyridinium chlorochromate (0.30 g, 1.4 mmol). The resulting mixture was stirred at room temperature for three hours before filtering and washing the residues with ether. The residual oil on evaporation was purified by chromatography (eluant: ethyl acetate - petrol) to give the **lactone** (29) as pale yellow crystals (90 mg, 62%), m.p. 78°C after recrystallisation from ethyl

acetate-petrol; (Found: C, 53.95; H, 5.3. $C_7H_8O_4$ requires C, 53.85, H, 5.1); ν_{max} ($CHCl_3$) 1725 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.93 (1H, dd, J 9.9, 4.95 Hz, 3-H), 6.20 (1H, d, J 9.9 Hz, 2-H), 5.33 (1H, m, 4-H), 4.52 (2H, m, 5α-H and 5β-H) and 2.12 (3H, s, $-OCOCH_3$); δ_C ($CDCl_3$) 170.0 (lactone C=O), 161.8 (ester C=O), 140.8, 124.6 (each, =CH), 69.0 (4-H), 61.9 (5-C) and 20.7 ($-OCO\underline{CH}_3$); m/z (E.I.) 126 ($M-CH_2O$), (C.I.) 157 ([M+1]) and 96 (M-AcOH).

Base-catalysed reaction of lactone (29) with methanol

To a solution of the lactone acetate (29) in methanol was added a catalytic quantity of potassium carbonate and stirred for one hour at room temperature, when complete reaction was observed by tlc to a less mobile material which appeared to be ring-cleaved product (32) from consideration of its mass spectra; m/z (C.I.) 147 ([M+1]), 128, 115 ([M+1]-MeOH).

Reaction of the (4S)-5-O-acetyl-4,5-dihydroxy-pent-2-enal (28) with ethanedithiol - A preliminary investigation

To a solution of the aldehyde (28) (36.3 mg, 0.22 mmol) in dry dichloromethane (5 ml) was added ethanedithiol (0.036 ml, 0.44 mmol). This mixture was equilibrated in an ice-bath before addition of a catalytic quantity of boron trifluoride etherate. After 30 minutes, tlc analysis revealed complete conversion to a more mobile material which was recovered by adsorbing the reaction mixture directly onto silica and eluting through silica gel (eluant: 1:1 ethyl acetate:petrol) giving the yellow semisolid product (30) (42.2 mg, 83.5%), ν_{max} (CH_2Cl_2) 3600 (OH) and 1735 cm^{-1} (C=O); δ_H

($CDCl_3$) 5.86 (1H, m, 2-H), 5.63 (1H, m, 3-H), 5.03 (1H, d, J 9 Hz, 1-H), 4.39 (1H, m, 4-H), 4.15 (1H, dd, J 11.5, 3.5 Hz, 5-H), 4.01 (1H, dd, J 11.5, 7.2 Hz, 5-H), 3.3 (3H, m), 2.8 (1H, m), 2.31 (1H, t) and 2.10 (3H, s, $-OCO\underline{CH}_3$); δ_C ($CDCl_3$) 171.1 (C=O), 133.0, 128.3 (each, =CH), 69.7 (CH), 67.6 (5-C), 53.1 (CH), 39.4 (2 x $-S\underline{CH}_2$) and 20.8 ($-OCO\underline{CH}_3$); m/z (C.I.) 217 ([M+1]$-H_2O$), 175 ([M+1]-HOAc) and 157 ([217]-HOAc).

Reaction of the alcohol (30) with trichloroacetonitrile

A solution of the allylic alcohol (30) (3.1 mg, 0.01 mmol) in dry ether (1 ml) was equilibrated in an ice-bath before addition of a catalytic quantity (< 1 mg) of sodium hydride. After five minutes an excess of trichloroacetonitrile (in ether) was added dropwise. TLC analysis after two hours, during which time the reaction was allowed to warm to room temperature, revealed complete reaction to a more mobile material. This material was recovered by evaporation of the solvent, re-solution in petrol containing a little methanol and re-evaporation. Chromatography (eluant: dichloromethane) afforded the **imidate** (31) (4.4 mg, 88%), ν_{max} (CH_2Cl_2) 1710 (C=O) and 1660 cm^{-1} (N=H); δ_H (400 MHz, $CDCl_3$) 8.4 (1H, br, N=H), 5.9 (1H, m, =CH), 5.75 (1H, m, =CH), 5.0 (1H, d, J 5.5 Hz, 1-H), 4.4 (2H, m, 5α-H and 5β-H), 3.2 (5H, m, SCH_2CH_2S + 4-H) and 2.1 (3H, s, $-OCOCH_3$).

Acidic hydrolysis of the methyl 2,3-dideoxy-4-O-(2',2',2'-trichloroacetimidoyl)-D-glycero-pent-2-enopyranosides (8)

A solution of the trichloroacetimidoyl methyl glycosides (8)

(0.388 g, 1.4 mmol) in a water (25 ml) THF (4 ml) mixture containing a catalytic quantity of Amberlyst 15 H^+ resin was stirred overnight at room temperature. TLC analysis showed complete conversion to several less mobile materials. These were recovered by saturating the reaction mixture with NaCl and exhaustive extraction with dichloromethane (6 x 50 ml). The dichloromethane extract was dried ($MgSO_4$) and evaporated *in vacuo* to yield several fractions on chromatography (eluant: ethyl acetate-petrol), the most mobile of which appeared to have undergone a dehydration to give **4-(2',2',2'-trichloroacetamido)-2*H*-pyran** (35) (31.4 mg, 9.2%), ν_{max} ($CHCl_3$) 3380 (NH) and 1715 cm^{-1} (C=O), δ_H ($CDCl_3$) 7.40 (1H, dd, *J* 1.8, 0.9 Hz, 6-H), 6.34 (1H, dd, *J* 3.3, 1.8 Hz, 5-H), 6.29 (1H, dd, 3.1, 0.6 Hz, 3-H), 4.60 (2H, s, 2α-H and 2β-H) and 2.15 (1H, br, NH); δ_C ($CDCl_3$) 142.5, 110.3, 107.7 and 57.4; m/z: (C.I.) 242 ([M+1]), 178, 162, 126. The more polar fractions were recovered in lower quantities and only 15.8 mg of hydroxylic material was obtained.

2,3,4-Trideoxy-4-thiocyanato-L-*glycero*-pent-2-enopyranoses (36)

A suspension of the glycoside (21) (150.3 mg, 0.88 mmol) was made in distilled water (5 ml) containing a catalytic quantity of Amberlyst 15 acid resin and the mixture stirred at room temperature until the analysis showed consumption of starting material and the formation of less mobile material (*ca*. 2 days). These products were recovered by filtration of the resin, lyophilisation and freed from remaining starting material (6.9 mg) by column chromatography (eluant: ethyl acetate-petrol) to give crystalline **lactol** (36)

(69.9 mg, 56.9%), for which a satisfactory elemental analysis was not obtained; m.p. 91-93°C; ν_{max} (CH_2Cl_2) 3560 (OH) and 2150 cm^{-1} (SCN); δ_H ($CDCl_3$) 6.2-6.0 (2H, m, 2-H and 3-H), 5.5 (1H, dd, 1-H), 4.5-4.2 (2H, m, 5-H and OH), 4.1-4.0 (1H, m, 5-H) and 3.8-3.7 (1H, m, 4-H); δ_C ($CDCl_3$) 130.7, 125.5 (each, =CH), 94.9 (SCN), 88.9 (1-C), 62.1 (5-C) and 42.2 (4-C); m/z: (E.I.) 140 (M-OH), 111 (M-HCOOH), (C.I.) 158 ([M+1]), 140 ([M+1]-H_2O), 111 ([M]-HCOOH) and 99 ([M+1]-HSCN).

(4R)-5-Hydroxy-4-thiocyanato-pent-2-enoic acid, δ-lactone (37)

To a solution of the lactol (36) (80 mg, 0.51 mmol) in dichloromethane (5 ml) was added pyridinium chlorochromate (0.16 g, 0.75 mmol) and the mixture left to stir overnight at room temperature, when a second portion of pyridinium chlorochromate (0.16 g, 0.75 mmol) was added and stirred for a further 8 hours. The product was recovered by column chromatography through silicate (eluant: ethyl acetate-petrol) giving recovered starting material (51.4 mg) and **lactonic material** (37) (14.8 mg, 52.4% based on recovered starting material), ν_{max} (CH_2Cl_2) 2150 (SCN) and 1735 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.95 (1H, m, 3-H), 6.29 (1H, dd, J 9.7, 1.1 Hz, 2-H), 4.80 (1H, dd, J 12.6, 3.8 Hz, 5-H), 4.66 (1H, m, 5-H) and 4.13 (1H, m, 4-H); δ_C ($CDCl_3$) 140.4 (2-C), 125.1 (3-C), 69.8 (5-C), 40.3 (4-C); m/z: (E.I.). 155 (M), 125 (M-CH_2O), 111 (M-CO_2), 97 (M-SCN) (C.I.) 156 ([M+1]) and 97 ([M+1]-HSCN).

Thermal rearrangement of the thiocyanate (39) - Attempted formation of (2S)-5-hydroxy-2-isothiocyanato-pent-3-enoic acid, δ -lactone (38).

A solution of the 2,3-unsaturated lactone (37) (17.0 mg, 0.11 mmol) in toluene (2 ml) was refluxed for ca. 30 hours, when tlc analysis showed conversion of starting material to several more mobile materials. Chromatography of the residues gave several fractions in poor yield (3.0 mg in total). Only one of the products (1.8 mg) has proved identifiable, appearing to be **5-hydroxy-2-isothiocyanato-pent-2-enoic acid, δ -lactone** (39) δ_H ($CDCl_3$) 6.62 (1H, t, J 4.8 Hz, 3-H), 4.45 (2H, t, J 6.4 Hz, 5α-H and 5β-H) and 2.61 (2H, td, J 6.3, 4.8 Hz, 4α-H and 4β-H); m/z: (E.I.) 155 (M) and 125 ($M-CH_2O$).

Methyl 2,3,4-trideoxy-2-methylcarbamoyl-D-glycero-pent-3-enopyranosides (40)

A solution of the trichloroacetamide (9) (2.52 g, 9.2 mmol) in methanol (25 ml) containing sodium hydroxide (1% w/w MeOH) was heated at reflux for 5-6 hours when complete reaction to a less mobile product was achieved. The product was recovered by preadsorption onto silica gel and elution through silica (eluant: 1:1 ethyl acetate in petrol) giving the methylcarbamate derivative (40) (1.36 g, 79%), m.p. 67-70°C, (Found: C, 50.65; H, 6.8; N, 6.95. $C_8H_{13}NO_4$ requires C, 51.3; H, 6.95, N, 7.5); ν_{max} (CH_2Cl_2) 3430 (NH) and 1700 cm^{-1} (C=O); δ_H ($CDCl_3$) 5.95 (1H, m, =CH), 5.78 (1H, m, =CH), 4.79 (1H, br, NH), 4.68 (1H, s, 1-H), 4.17 (1H, m, 5-H), 4.04 (2H, m, 2-H and 5-H), 3.68 (3H, s, OMe) and 3.48 (3H, s,

OMe); δ_C ($CDCl_3$) 155.7 (C=O), 128.7, 121.7 (each, =CH), 99.9 (1-C), 58.5 (5-C), 55.5 ($O\underline{C}H_3$), 51.5 ($O\underline{C}H_3$) and 46.6 (2-C); m/z: (E.I.) 156 (M-OMe), 127 (M-HCOOMe), (C.I.) 188 ([M+1]).

1-O-Methoxycarbonyl 2-amino-2,3,4-trideoxy-D-glycero-pent-3-eno-pyranosides (43)

A solution of the trichloroacetamide (9) (10.1 g, 36.8 mmol) in 1% methanolic NaOH solution was stirred at room temperature for several days when tlc analysis suggested the formation of the carbamate (40). However, on product recovery by neutralisation (2M HCl) and pre-adsorption onto silica, yellowing was observed and very little methylcarbamate (40) was eluted. Instead, an amount of polar material was eluted by ethanolic ethyl acetate, which on recrystallisation from ethyl acetate-petrol gave a white crystalline material (< 3.5 g, 55%) m.p. 117-119°C. This material was found to give a basic solution in water and might be the amine (43) formed by hydrolysis. ν_{max} (Nujol) 1650 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.59 (2H, br, NH_2), 6.03 (1H, m, =CH), 5.90 (1H, m, =CH), 4.86 (1H, s, 1-H), 4.20 (2H, s, 5α-H and 5β-H) and 3.48 (4H, brand s, 2-H + -OMe); δ_C ($CDCl_3$) 164.8 (C=O), 130.9, 120.3 (each, =CH), 98.6 (1-C), 60.5 (5-C), 56.1 (OMe) and 47.2 (2-C); m/z: (E.I.) 69 (M-HCOOC(O)OMe), (C.I.) 140, 130 ([M+1]-CO_2), 98 ([M+1]-HOC(O)OMe). This material did not give a satisfactory elemental analysis.

1-O-Methoxycarbonyl 2-acetamido-2,3,4-trideoxy-D-glycero-pent-3-enopyranosides (44)

To a solution of the amine (43) (104 mg, 0.6 mmol) in

dichloromethane (5 ml) was added pyridine (0.145 ml, 1.8 mmol) and acetic anhydride (0.085 ml, 0.9 mmol) and the mixture stirred for ca. two days at room temperature until complete conversion to a mobile material was observed by tlc analysis. The reaction mixture was washed with 2 M HCl (1 volume), $CuSO_4$ (aq) (1 volume), saturated $NaHCO_3$ (aq) (2 x 1 volume) and water (1 volume), dried ($MgSO_4$), evaporated in vacuo and chromatographed to yield the **methoxycarbonyl glycoside** (44) as a crystalline solid (36.5 mg, 28%), 87-88°C (from ethyl acetate-petrol). (A non-aqueous recovery procedure by direct chromatography resulted in a greater recovery - 52%). ν_{max} ($CDCl_3$) 3410 (NH) and 1640 cm^{-1} (C=O); δ_H ($CDCl_3$) 5.98 (1H, m, =CH), 5.85 (1H, brd, NH), 5.74 (1H, m, =CH), 4.65 (1H, s, 1-H), 4.30 (1H, m, 2-H), 4.19 (1H, m, 5-H), 4.04 (1H, m, 5-H), 3.47 (3H, s, OCOOMe) and 2.00 (3H, s, $NHCOCH_3$); δ_C ($CDCl_3$) 169.4 (C=O), 129.3, 121.3 (each, =CH), 99.8 (1-C), 58.7 (5-C), 55.8 (-OMe), 45.2 (2-C) and 23.1 ($-COCH_3$); m/z: (E.I.) 111 (M-HCOOCOOMe), (C.I.) 172 ([M+1]$-CO_2$), 140 ([M+1] -HOC(O)OMe) and 111 (M-HCOOCOOMe).

Methyl 2,3,4-trideoxy-2-amino-D-glycero-pent-3-enopyranosides (41)

A solution of the trichloroacetamide (9) (1.18 g, 4.3 mmol) in 1% aqueous NaOH solution (25 ml) was stirred at room temperature for ca. 30 hours when complete deprotection was observed to a less mobile product by tlc analysis. Saturation of the aqueous solution with NaCl and exhaustive extraction with dichloromethane (6 x 1 volume) gave an extract which was dried ($MgSO_4$) and evaporated in vacuo to yield the **amine** (41) as a yellow oil (0.35 g, 63%). ν_{max} ($CHCl_3$) 3360, 3200 cm^{-1} (NH_2); δ_H ($CDCl_3$) 5.82-5.72 (2H, m, each,

=CH), 4.42 (1H, d, J 3.1 Hz, 1-H), 4.25-4.06 (2H, m, 5α-H and 5β -H), 3.49 (3H, s, -OMe), 3.15 (1H, m, 2-H) and 1.71 (2H, br, NH_2, exch.); δ_C ($CDCl_3$) 126.4, 126.2 (each, =CH), 103.9 (1-C), 61.1 (5-C), 55.9 ($-OCH_3$) and 48.5 (2-C); m/z: (C.I.) 98 ([M+1]-MeOH).

Methyl 2,3,4-trideoxy-2-acetamido-D-glycero-pent-3-enopyranosides (42)

To a solution of the amine (41) (0.350 g, 2.7 mmol) in dry dichloromethane (20 ml) was added pyridine (0.66 ml, 8.1 mmol), then acetic anhydride (0.384 ml, 5.4 mmol) and the mixture stirred for 2 days at room temperature when the reaction was complete by gc-analysis. The reaction mixture was washed with 2 M HCl (1 volume), saturated $CuSO_4$ (aq) (1 volume), saturated $NaHCO_3$ (aq) (1 volume), water (1 volume) and saturated brine (1 volume), dried ($MgSO_4$) and evaporated in vacuo to give a colourless solid (150 mg) which was found to be readily water soluble so the aqueous extracts were saturated with NaCl and re-extracted with $CHCl_3$ (6 x 1 volume) whereby a further 300 mg of solid was recovered. The crude **acetamide** (42) (0.426 g, 91.7%) was recrystallised from ethyl acetate-petrol as colourless crystals, m.p. 89-90°C, (Found: C, 56.2; H, 7.9; N, 8.1, $C_8H_{13}NO_3$ requires C, 56.1; H, 7.6; N, 8.2); ν_{max} (CH_2Cl_2) 3410 (NH) and 1655 cm^{-1} ($NHCOCH_3$ C=O); δ_H ($CDCl_3$ 6.0-5.8 (3H, m, 3-H, 4-H and NH), 4.65 (1H, s, 1-H), 4.3-4.2 (1H, m, 2-H), 4.2-4.0 (2H, m, 5α-H and 5β-H), 3.5 (3H, s, -OMe) and 2.0 (3H, s, $-COCH_3$); δ_C ($CDCl_3$) 169.4 (C=O), 129.2, 121.3 (each, =CH), 99.7 (1-C), 58.6 (5-C), 55.8 (OCH_3), 45.2 (2-C) and 23.1 ($-CO\underline{C}H_3$); m/z: (E.I.) 111 (M-HCOOMe), (C.I.) 172 ([M+1]) and 140 ([M+1] -MeOH).

2,3,4 Trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranoses (45)

A solution of the trichloroacetamide (9) (1.92 g, 7 mmol) in 2M HCl (25 ml) was refluxed until tlc analysis revealed loss of starting material and formation of less-mobile material (not more than three hours). The products were recovered by neutralisation (NaOH (aq)), saturating the neutral solution with NaCl and exhaustive extraction with $CHCl_3$ (6 x 1 volume). The combined organics were dried ($MgSO_4$). The residues on concentration in vacuo were purified by chromatography (eluant: ethyl acetate - petrol) to give the **2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranoses** (45) as an anomeric mixture (Found: C, 32.6; H, 3.15; N, 5.4, $C_7H_8NO_3Cl_3$ requires C, 32.3; H, 3.10; N, 5.4); ν_{max} (CH_2Cl_2) 3600 (OH), 3420 (NH) and 1710 cm^{-1} (C=O); δ_H ($CDCl_3$) 7.01, 6.7 (1H, br, NH) 6.1, 6.0 (1H, two m, =CH), 5.8, 5.7 (1H, two m, =CH), 5.3, 5.16 (1H, two d, 1-H), 4.7-4.6, 4.1 (1H, two m, 2-H), 4.45-4.2 (2H, two m, 5-H) and 3.2 (1H, br, OH); δ_C ($CDCl_3$) 162.1 (C=O), 130.7, 128.8, 122.0, 120.4 (each, =CH), 92.6, 89.8 (each, 1-C - ratio 1.24:1), 60.6, 60.0 (each, 5-C) and 48.8, 47.8 (each, 2-C); m/z: (E.I.) 213 (M-HCOOH), 178 (M-Cl), (C.I.) 260 ([M+1]), 242 ([M+1]-H_2O), 208, 190 and 144.

2,3,4-Trideoxy-2-acetamido-D-glycero-pent-3-enopyranoses (46)

A solution of the glycoside (42) (2.52 g, 14.7 mmol) in 2 M HCl (30 ml) was stirred overnight at room temperature when tlc analysis revealed complete deprotection to a less mobile material. This material was recovered by neutralisation of the aqueous solution

(with aqueous NaOH), saturation of the reaction mixture with NaCl and exhaustive extraction with $CHCl_3$ (6 x 50 ml). The combined organic extracts were dried ($MgSO_4$) concentrated *in vacuo* onto silica gel and purified chromatographically (eluant: ethyl acetate) to give the **lactol** anomer mixture (46) as a yellow oil (1.94 g, 83.8%). One anomer was crystallised from ethyl acetate-petrol as colourless crystals, m.p. 124-125°C; (Found: C, 52.6; H, 7.1; N, 8.8, $C_7H_{11}NO_3$ requires C, 53.5; H, 7.0; N, 8.9); ν_{max} ($CDCl_3$) 3600 (OH), 3440 (NH) and 1730 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.62 (1H, d, NH), 5.97-5.95 (2H, m, =CH and -OH), 5.75-5.7 (1H, m, =CH), 4.95 (1H, dd, 1-H), 4.4-4.0 (3H, m, 5α-H, 5β-H and 2-H), 2.69 (1H, s, OH) and 1.99 (3H, s, $COCH_3$); δ_C ($CDCl_3$) 170.4 (C=O), 129.1, 122.4 (each, =CH), 93.8 (1-C), 60.2 (5-C), 47.7 (2-C) and 23.1 ($-COCH_3$); m/z: (E.I.) 111 (M-HCOOH), (C.I.) 158 ([M+1]) and 140 ([M+1]$-H_2O$).

2,3,4-Trideoxy-2-methylcarbamoyl-D-*glycero*-pent-3-enopyranoses (47)

A solution of the glycoside (40) (0.50 g, 2.67 mmol) in 2 M HCl (40 ml) was stirred for 24 hours at room temperature when complete deprotection was suggested by tlc analysis. The product was recovered by careful neutralisation of the reaction mixture (aq. NaOH), saturation of the aqueous solution with sodium chloride and exhaustive extraction with $CHCl_3$ (6 x 1 volume). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (eluant: ethyl acetate - petrol) to give the **lactols** (47) (0.285 g, 81.9% based on recovered starting material) as a colourless crystalline anomeric mixture; one anomer could be crystallised from ethyl acetate-petrol, m.p. 122-125°C, (Found: C,

48.7; H, 6.5; N, 8.05. $C_7H_{11}NO_4$ requires C, 48.55; H, 6.6; N, 8.1); ν_{max} ($CHCl_3$) 3600 (OH), 3440 (NH) and 1700 cm^{-1} (C=O); δ_H ($^2H_6DMSO$) 6.04 (1H, d, J 5 Hz, NH exch.), 5.95 (1H, d, J 10.6 Hz, =CH), 5.8-5.7 (2H, m, =CH and -OH exch.), 4.97 (1H, dd, J 5, 3 Hz, 1-H), 4.36-4.30 (1H, dd, J 16.8, 2.2 Hz, 5-H), 4.06 (1H, dd, J 16.5, 2 Hz, 5-H), 3.97 (1H, br, 2-H) and 3.66 (3H, s, -OMe); δ_C ($^2H_6DMSO$) 128.8, 122.6 (=CH), 93.7 (1-C), 60.2 (5-C), 51.9 (2-C) and 48.9 (-OMe); m/z: (E.I.) 127 (M-HCOOH), (C.I.) 174 ([M+1]) and 156 ([M+1]$-H_2O$).

Attempted formation of 2,3,4-trideoxy-2-isothiocyanato-L-glycero-pent-3-enopyranoses (48) by acid hydrolysis of the glycosides (22)

A solution of the isothiocyanate glycoside (22) (100 mg, 0.585 mmol) in 2 M HCl (5 ml) was stirred at room temperature for an extended period, without evident reaction; elevation to reflux temperature for 1 hour caused discolouration but tlc analysis suggested reaction to a less mobile material which was isolated by neutralisation, NaCl saturation and exhaustive extraction as a clear oil (24.4 mg). This material was not the expected product and remained unidentified, ν_{max} (CH_2Cl_2) 3380 (NH) and 1685 cm^{-1} (C=O); δ_H (CDl_3) 6.52 (1H, br, NH), 6.2-6.1 (1H, m, =CH), 5.8-5.9 (1H, m, =CH), 5.75-5.7 (1H, d, J 4.75 Hz, 1-H), 4.4-4.0 (3H, m, 5α-H, 5β-H and 2-H), 3.7 (1H, b) and 3.5 (1H, two s); δ_C (CDl_3) 129.8, 121.4 (each, =CH), 98.1 (1-C), 82.0 (CH), 62.9 (5-C), 51.6 (CH); m/z: (E.I.) 157 (M), 128, 111, (C.I.) 158 ([M+1]), 140 ([M+1]$-H_2O$), 128, 124 and 81.

Oxidation of lactol (45) with pyridinium chlorochromate: Formation of (2R)-5-hydroxy-2-(2',2',2'-trichloroacetamido)-pent-3-enoic acid, δ-lactone (49)

To a solution of the lactol (45) (0.40 g, 1.5 mmol) in dry dichloromethane (20 ml) was added pyridinium chlorochromate (4.96 g, 2.3 mmol) and the mixture stirred at room temperature overnight when the products were recovered by diluting the mixture in ether (or dichloromethane) and filtering through Celite with exhaustive washing. Chromatography of the residual dark oil on evaporation in vacuo gave an oil containing lactone (49) and unreacted alcohol (45) which on repeated chromatography (eluant: 1:3 to 1:1 ethyl acetate:petrol) were separable. (The lactone (49) was I_2 active on tlc, but not revealed by H_2SO_4/MeOH). The lactone (49) was a solid (110 mg, 50.4% based on recovered starting material) which could be recrystallised from ethyl acetate-petrol as white crystals, m.p. 141°C, (Found: C, 32.6; H, 2.35; N, 5.5. $C_7H_6NO_3Cl_3$ requires C, 32.5; H, 2.3; N, 5.4); ν_{max} (CH_2Cl_2) NO-OH, 3410 (NH), 1750 (lactone C=O) and 1725 cm^{-1} (amide C=O); δ_H ($CDCl_3$) 7.63 (1H, brd, NH), 6.20 (1H, m, =CH), 6.15 (1H, m, =CH) and 5.0-4.9 (3H, m, 2-H, 5α-H and 5β-H); δ_C ($CDCl_3$) 167, 162 (each, C=O), 126.0, 124.8 (each, =CH), 68.4 (5-C) and 50.2 (2-C); m/z: (E.I.) 213 ($M-CO_2$), 140 ($M-CCl_3$), 96 ($M-NHCOCCl_3$) and (C.I.) 258 ([M+1]).

Note: less polar side-products obtained, in low yield, from a similar oxidation on lactol (47) showed ν_{max} (CH_2Cl_2) 3680 (OH), 3480 (NH), 1760 and 1730 cm^{-1} (C=O); δ_H ($CDCl_3$) 7.84 (1H, br), 7.39 (1H, s), 4.98 (2H, s), 3.83 (3H, s, -OMe) and 1.75 (1H, b); m/z: (E.I.) 185, 155, 127, 99 and 68. Some aldehydic material was also recovered δ_H ($CDCl_3$) 8.96 (1H, d, J 10.3 Hz, CHO), 7.27 (2H, m, each =CH) and 3.85 (3H, s, -OMe).

Formation of (2R)-5-hydroxy-2-(2',2',2'-trichloroacetamido)-pent-3-enoic acid, δ -lactone (49) by lactol oxidation with pyridinium dichromate

To a solution of the lactol (45) (1.49 g, 5.72 mmol) in dry dichloromethane (150 ml) was added some ground, freshly-activated pyridinium dichromate (4.3 g, 11.44 mmol) with a catalytic quantity of acetic acid (2-3 drops) and the mixture stirred overnight over 4A° molecular sieves, when a second portion of pyridinium dichromate (4.3 g, 11.44 mmol) was added. After a further reaction period (6-8 hours), the reaction mixture was filtered through Celite (with exhaustive washing) and the residue on evaporation purified by careful chromatography through silica (eluant: ethyl acetate-petrol). Again unoxidised lactol (45) was recovered (0.68 g) as well as lactone (49) (0.42 g, 52% based on recovered starting material).

More mobile side-products were recovered from the chromatographic separation in low yield and one tentatively identified as 5-(2',2',2'-trichloroacetamide)-2-H-pyran (51), δ_H ($CDCl_3$) 6.7 (1H, br, 6-H), 6.1 (1H, t, J 12-13 Hz, =CH), 5.8 (1H, m, =CH), 4.2 (2H (+ additional 1H, unassigned), m, 2α-H and 2β-H) and 3.50 (1H, s, NH); m/z: (E.I.) 242 (M), 213 and 180.

Reaction of the methylcarbamoyl lactol (47) with N-bromosuccinimide

N-Bromosuccinimide (0.09 g, 0.52 mmol) was added portionwise over ca. 20 minutes to a refluxing solution of the lactol (47) (90 mg, 0.52 mmol) in ethyl acetate (2 ml). During the addition bromine appeared to be liberated and tlc analysis revealed consumption of

starting material and formation of a complicated mixture of products which were recovered by washing with 10% aqueous potassium iodide (1 volume), 15% aqueous sodium thiosulphate (1 volume) and 10% aqueous sodium bicarbonate (1 volume). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a residue which revealed a streak of products on tlc analysis. Chromatographic separation produced three fractions, the components of which were tentatively assigned structures by consideration of their mass spectra, revealing extensive bromination.

The first product eluted was possibly 1,2-(2'-methoxy-1'-oxa-3'-azaprop-2'-enyl) 2,3,4-trideoxy-α-D- glycero-pent-3-enopyranoside (54), m/z: (E.I.) 155 (M), 123 (M-MeOH), (C.I.) 156 ([M+1]) and 124 ([M+1]-MeOH). The next fraction contained a mixture assigned as 4-bromo-2,4-dideoxy-3,2-(2'-methoxy-1'-oxa-3'-azaprop-2'-eno)-L-lyxo-pentopyranosidyl bromide (56) and the 4-bromo-2,4-dideoxy-3,2-(2'-methoxy-1'-oxa-3'-azaprop-2'-eno)-L-lyxo-pentopyranoses (55), m/z: (E.I.) 222, 200, 112, (C.I.) 330, 314 ([M+1] for (56)), 306, 298, 266 and 252 ([M+1] for (55)). Finally a material was eluted which was tentatively identified as 4,5-dibromo-2,4-dideoxy-3,2-(2'-methoxy-1'-oxa-3'-azaprop-2'-eno)-L-lyxo-pentopyranosidyl bromide (57), m/z (E.I.) 311, (C.I.) 391 ([M+1]), 312 ([M+1] -Br) and 232 ([312] - HBr).[218]

Reaction of lactol (47) with N-iodosuccinimide: Attempted formation of (2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enoic acid, δ-lactone (61)

To a solution of the lactol (47) (100 mg, 0.58 mmol) in dry

dichloromethane (5 ml) was added tetra-n-butylammonium iodide (0.213 g, 0.58 mmol) then N-iodosuccinimidate (0.52 g, 2.3 mmol) and the resulting solution stirred overnight at room temperature when tlc analysis revealed complete consumption of starting material. Then products were recovered by washing with 10% aqueous sodium thiosulphate (1 volume) (and backwashing with a volume of $CHCl_3$). The organic phases were combined, dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (0.32 g) which could be separated by chromatography (eluant: ethyl acetate in petrol) to give a low recovery of the lactone (61) (24.8 mg, contaminated with succinimide), a non-polar side-product (5.9 mg, 6%), tentatively identified as **3-methylcarbamoyl-pyran-2-one** (58); ν_{max} (CH_2Cl_2) 3400 (NH), 1710 (C=O) and 1645 cm^{-1} (diene); δ_H ($CDCl_3$) 7.87 (1H, dd, J 8, 2 Hz, 6-H), 7.44 (1H, br, NH), 7.23 (1H, dd, J 6, 2 Hz, 4-H), 6.30 (1H, dd, J 8, 6 Hz 5-H) and 3.79 (3H, s, -OMe); m/z: (E.I.) 169 (M), 137 (M-MeOH), as well as a major, unidentified polar contaminant.

Attempted formation of (2R)-5-hydroxy-2-(2',2',2'-trichloro-acetamido)-pent-3-enoic acid, δ-lactone (49) by lactol oxidation with active MnO_2

Active manganese dioxide (1 g, 11.5 mmol) was added to a solution of the lactol (45) (84.9 mg, 0.33 mmol) in chloroform (10 ml) and the mixture stirred overnight at room temperature. The reaction proceeded to give a more mobile material (R_f > 0.5 in 20% ethylacetate-petrol) which was recovered by adsorption onto silica and chromatography (eluant: 1:9 ethylacetate:petrol) as a white

solid (17 mg, 20.3%), m.p. 74°C (with decomposition) which appeared to be the product of dehydrogenation, **3-(2',2',2'-trichloro-acetamido)pyran-2-one** (59); λ_{max} (EtOH) 307 nm, ε_{max} 1114; ν_{max} (CH_2Cl_2) 3360 (NH) and 1710 cm^{-1} (C=O); δ_H ($CDCl_3$) 9.20 (1H, br, NH), 8.23 (1H, dd, J 7, 1.8 Hz, 6-H), 7.35 (1H, dd, J 5.15, 1.8 Hz, 4-H) and 6.39 (1H, dd. J 7, 5.2 Hz, 5-H); m/z: (E.I.) 255 (M), 220 (M-Cl), 138 (M-CCl_3), (C.I.) 256 ([M+1]) and 138 ([M+1]-$HCCl_3$).

Attempted formation of (2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enoic acid, δ-lactone (61) by dehydrogenation of the lactol (47) over Pt

The catalyst was prepared by reducing Adam's catalyst (PtO_2) with H_2 (1 atm) in acetic acid, until H_2 uptake ceased.

The lactol (47) (80 mg, 0.4 mmol) was dissolved in dilute aqueous HCl solution (25 ml, pH 3) in a three-necked round-bottomed flask and to this was added the catalyst (100 mg approximately) and the reaction vessel immersed in a water-bath at 40°C. Oxygen was introduced via a sintered bubbler into the stirred, warm aqueous solution of the lactol. After 1 hour of oxygen passage the aqueous solution was decanted from the settled catalyst (with washing) and lyophilised overnight. Tlc analysis of the residue suggested incomplete reaction but reintroduction to the system gave no further reaction. Again freeze-drying gave a residue which could be separated by repeated chromatography (eluant: ethyl acetate - petrol) to give lactol (47) (15.8 mg) and a slightly more mobile product (22.6 mg) which appeared to have been dehydrated though not oxidised. ν_{max} ($CDCl_3$) NO-OH, 3440 (NH) and 1700 cm^{-1} (C=O); δ_H

($CDCl_3$) 6.0 (1H, dt, J 11, 2 Hz, =CH) 5.7 (1H, m, =CH), 4.95 (1H, d, J 12 Hz, 1-H), 4.3 (1H, d, J 17.2 Hz, 5-H), 4.05 (1H, m, 5-H), 4.0 (1H, m, 2-H) and 3.68 (3H, s, -OMe); δ_C ($CDCl_3$) 156.3 (C=O), 129.6, 120.7 (each, =CH), 94.0 (1-C), 58.9, 52.3 and 46.7 (each, CH and -OMe); m/z: (E.I.) 171, 156 (M). This material remains uncharacterised.

2(R)-5-Hydroxy-2-methylcarbamoyl-pent-3-enoic acid, δ -lactone (61)

The lactol (47) (0.60 g, 3.47 mmol) was chilled in an ice-salt bath, then dimethylsulphoxide (4.2 ml) and acetic anhydride (2.75 ml) added to form a solution. This solution was then stored at 0°C overnight before being allowed to warm to room temperature in an ice-bath for a further 20 hours, until gc-analysis (at 130°C isotherm) showed complete consumption of the lactol (47). The solvents were then evaporated by Kugel-Rohr distillation (50°C, 0.5 mm Hg) and the remaining yellow oil purified by chromatography to give the conjugated lactone (62) (Rf: 0.6) (50.2 mg, 8.5%) **5-hydroxy-2-methylcarbamoyl-pent-2-enoic acid, δ -lactone** (62) as the most mobile product, ν_{max} (CH_2Cl_2) 3380 (NH) and 1710 cm^{-1} (C=O); δ_H ($CDCl_3$) 7.18 (2H, bt, J 4.7 Hz, 3-H and NH), 4.41 (2H, t, J 6.3 Hz, 5α-H and 5 -H), 3.74 (3H, s, $-OCH_3$) and 2.58 (2H, dt, J 6.3, 4.7 Hz); δ_C ($CDCl_3$) 162.2, 153.9 (each C=O), 125.3 (2-C), 120.6 (3-C), 67.2 (5-C), 52.5 (-OMe) and 23.1 (4-C); m/z: (E.I.) 171 (M), 139 (M-MeOH), (C.I.) 172 ([M+1]) and 156 ([M+1]-O). The second compound eluted (Rf: 0.5) was a mixture of **anomeric acetates** (60) (95.4 mg, 12.8%), δ_H ($CDCl_3$)- (anomeric mixture) - 6.2-5.7 (3H, m, 3-H, 4-H and NH), 4.8 (< 1H, m, 2-H), 4.6 (< 1H, m, 2-H),

4.2 (2H, m, 5α-H and 5β-H), 3.7 (3H, s, -OMe) and 2.15-2.1 (3H, two s, each $-COCH_3$); δ_C ($CDCl_3$) 169.3 (C=O), 128.8, 127.5, 123.6, 121.3 (each, =CH), 92.1, 89.9 (each, 1-C), 61.7, 60.3 (each, 5-H), 52.4 (-OMe), 46.1 (2-C) and 20.9 ($CO\underline{CH}_3$); m/z: (E.I.) 156 (M-OAc), 127 (M-HCOOAc), (C.I.) 172 (M-$COCH_3$), 156 ([M+1]-HOAc) and 127 (M-HCOOAc).

The most polar material eluted was the desired **lactonic** product (61) (Rf: 0.25) (0.45 g, 77%)* which crystallised from a clear oil when stored in the refrigerator, m.p. 81-83°C, $[\alpha]_D$ ($CHCl_3$) -5.6° (86.9 mg in 10 ml); (Found: C, 48.9; H, 5.7; N, 8.2. $C_7H_{10}NO_4$ requires C, 49.2; H, 5.3; N, 8.2); ν_{max} (CH_2Cl_2) 3420 (NH), 1750 (lactone C=O) and 1725 cm^{-1} (carbamate C=O); δ_H ($CDCl_3$) 6.12-6.06 (1H, m, =CH), 6.05-5.98 (1H, dt, $\underline{J}$ 9.5, 2 Hz, =CH), 5.62 (1H, br, NH, exch.), 5.0-4.8 (2H, m, 5α-H and 5β-H), 4.76 (1H, m, 2-H) and 3.74 (3H, s, -OMe); δ_C ($CDCl_3$) 177.9 (C=O lactone), 168 (C=O carbamate), 127.9, 123.8 (each, =CH), 68.2 (5-C), 52.6 (2-C) and 49.9 (-OMe); m/z: (E.I.) 139 (M-MeOH), 127 (M-CO_2), 112 (M-COOMe), (C.I.) 172 ([M+1]), 140 ([M+1]-MeOH) and 127 (M-CO_2).

Formation of 2,3,4-trideoxy-2-methylcarbamoyl-D-$\underline{glycero}$-pent-3-enopyranoses (47) by acetate hydrolysis

A solution of the anomeric acetate (60) (1.40 g, 6.5 mmol) in 2 N aqueous HCl (10 ml) was stirred for $\underline{ca}$. 3 hours at room temperature when tlc analysis showed reconversion to the lactol

* The yield of the lactone here was exceptional and was more commonly in the region of 60%.

(47). The lactol was recovered in the standard fashion (neutralised, NaCl saturated and exhaustively extracted with $CHCl_3$) and purification by column chromatography gave material identical to the synthetic lactol (47) (0.80 g, 70.8%).

Attempted formation of methyl (Z)-(2R)-5-dimethylphosphono-2-(2',2',2'-trichloroacetamido)-pent-3-enoate (63) by Arbusov lactone cleavage

A solution of the lactone (49) (78.8 mg, 0.3 mmol) in freshly-distilled trimethylphosphite (2 ml) was refluxed until gc-analysis revealed consumption of starting material (24 hours). The crude mixture was subjected to gc-ms analysis (Run conditions: 100-280°C, 15°C per minute) and tentative structural type assignments made as follows:

Peak One (Scan #245) (2R)-2-(2' 2'-Dichloroacetamido)-5-hydroxy-pent-3-enoic acid, δ-lactone (65) m/z: 223 (M) and 140 ($M-CCl_2H$).

Peak Two (Scan #251) (2R)-2-(2',2'-Dichloro-O-methylacetamido)-5-hydroxy-pent-3-enoic acid, δ-lactone (64) m/z: 237 (M) and 202 (M-Cl).

Peak Three (Scan #343). Methyl (Z)-(2R)-2-(2',2'-dichloro-O-methylacetamido)-5-dimethylphosphono-pent-3-enoate (66) m/z 361 (M), 325 (M-HCl) and 302 (M-COOMe).

Reaction of lactone (49) by Michaelis-Becker lactone cleavage with sodium dimethylphosphite

To hot, oven-dried glassware was added sodium hydride (8 mg,

0.33 mmol) and the reaction vessel then flushed cold with N_2. The sodium hydride was then suspended in freshly-distilled THF (3 ml) and dimethylphosphite (0.017 ml, 0.17 mmol) in THF (1 ml) added. A short time (5-10 minutes) was allowed for formation of the anion then the mixture chilled to 0°C and equilibrated before dropwise addition of the lactone (49) (38.7 mg, 0.15 mmol) in THF (1 ml). The reaction mixture was allowed to warm to room temperature over four hours, during which time the reaction darkened slowly to a black solution. The reaction was then quenched with saturated aqueous NH_4Cl (1 ml) and the precipitated white solid filtered. The filtrate was evaporated and the residues extracted with $CHCl_3$ and dried ($MgSO_4$). The material was then partitioned into aqueous NH_3 and the aqueous layer lyophilised, then passed down a pre-washed ion-exchange resin in H_2O and again lyophilised. The materials produced in this reaction remain largely uncharacterised but mass spectra of the aqueous-partitioned material suggests reaction at the sidechain trichloro-centre and concomitant conjugation giving 2-(2',2'-dichloro-2'-dimethylphosphono-acetamido)-5-hydroxy-pent-2-enoic acid, δ-lactone (67), m/z: (E.I.) 301 ($M-CH_2O$), (C.I.) 332 [M] and 222 [$M-HP(O)(OMe)_2$].

Attempted formation of ethyl (Z)-(2R)-5-diethylphosphono-2-methyl-carbamoyl-pent-3-enoate (69) by Arbusov lactone cleavage

A solution of the lactone (61) (87 mg, 0.51 mmol) in distilled triethylphosphite (from Na metal) (2 ml) was refluxed for 24 hours when gc-analysis revealed complete conversion of the starting material. The crude mixture was analysed by combined gc-ms

(conditions: 100-280°C, 15°C per minute) and possible structures assigned to the products.

Peak One (Scan #288) 5-Hydroxy-2-methylcarbamoyl-pent-2-enoic acid, δ-lactone (62). m/z: 171 (M), 139 (M-MeOH), 111 (M-COOMe) and 109 ([139] $-CH_2O$).

Peak Two (Scan #439) Phosphonate (69 or isomer) m/z: 305 (M-MeOH), 291 (M-EtOH), 264 (M-COOEt), 232 ([264]-MeOH), 188 [$(EtO)_2P(O)CH_2CH=CH_2$] and 161 [$EtOOCCH_2NHCOOMe$].

Peak Three (Scan #448) Phosphonate 969 or isomer). m/z: 337 (M), 306 (M-OMe), 305 (M-MeOH), 291 (M-EtOH), 264 (M-COOEt), 188 [$(EtO)_2P(O)CH_2CH=CH_2$] and 161 [$EtOOCCH_2NHCOOMe$].

Peak Four (Scan #454) Phosphonate (69 or isomer). m/z: 337 (M), 305 (M-MeOH), 291 (M-EtOH) and 176[$(M-(EtO)_2P(O)CH_2)$].

Peak Five (Scan #460) N-ethylated material (71). m/z: 365 (M), 333 (M-MeOH), 319 (M-EtOH) and 291 (M-COOEt).

Peak Six (Scan #484) Diethylphosphonyl 5-diethylphosphono-2-methylcarbamoyl-pent-3-enoate (72). m/z: 429 (M), 355 (M-NHCOOMe) and 221 ($M-COP(O)(OEt)_2-OMe$).

Products were recovered by rotary distillation of the solvents and separating the residues by chromatography on silica (eluant: 5% EtOH in EtOAc) to give an oil (58.7 mg) which seemed to be a mixture when examined by nmr and hplc. Separation was attempted by hplc (on ODS-C18, gradient of H_2O in CH_3CN, 5%-100% over 30 minutes with a 5 minute initial dwell) to give a major fraction (23.7 mg) which appeared to still be a two component mixture by nmr and gc (isothermal conditions at 250°C). Further separation was not attempted and structural assignment of the components of the

mixture has been attempted, e.g. for isomeric structures of the type (69, 70):- $_{H}$ ($CDCl_3$) 6.82 (1H, b, NH), 6.53 (1H, t, J 7.7 Hz), 5.8 (1H, m), 5.4 (1H, m), 4.88 (1H, b), 4.3-4.1 (6H, m), 3.71 (3H, two s, each -OMe), 2.6 (2H, m), 2.2 (2H, b), 1.9 (1H, m) and 1.3 (9H, c); $_{C}$ ($CDCl_3$) 164.4 (C=O), 133.6, 133.5, 129.6, 129.4, 123.1, 122.9 (each, =CH), 62.1, 62.0, 61.9, 61.8 (each, $PO\underline{CH_2}CH_3$), 61.7, 61.5 (each $CO\underline{CH_2}CH_3$), 55.4 (OCH_3), 52.6 (CH), 52.4 (OCH_3), 31.2, 29.1, 25.1, 23.0 (each 5-C), 21.6, 21.5 (each CH_2), 16.4, 16.3 (each $POCH_2\underline{CH_3}$), 14.15, 14.1 (each $COOCH_2\underline{CH_3}$); $_{p}$ 31.1, 26.0. GC-MS analysis of the two isomers (Run conditions: 230°C isothermal).

Peak One (Scan #210) Phosphonate (69 or E isomer). m/z: 305 (M-MeOH), 291 (M-EtOH), 264 (M-COOEt) and 161 $COOEtCH_2NHCOOMe$.

Peak Two (Scan #233) Phosphonate (70). m/z: 305 (M-MeOH), 291 (M-EtOH) and 176 ($M-(EtO)_2P(O)CH_2$).

Reaction of lactone (61) with trimethylphosphite containing trimethylphosphate - Attempted formation of methyl (Z)-(2R)-5-dimethylphosphono-2-methylcarbamoyl-pent-3-enoate (68)

A solution of the lactone (61) (10 mg, 0.05 mmol) in trimethylphosphite (1 ml) containing trimethylphosphate (0.25 ml) was heated at reflux for an extended period (> 30 hrs) and the reaction monitored by gc-analysis. No improved reaction to desired product (68) was observed, instead, conversion to a different product occurred (Peak Four below). The reaction mixture was analysed by gc-ms and tentative structures assigned on the basis of the mass spectra. (Run conditions: 100-280°C - 15°C per minute).

Peak One (Scan #157) N-Methyl (2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enoic acid, δ-lactone (73). m/z: 185 (M), 157 (M-CO) and 126 (M-COOMe).

Peak Two (Scan #176) 5-Hydroxy-2-methylcarbamoyl-pent-2-enoic acid, δ-lactone (62) - previously characterised.

Peak Three (Scan #195) (2R)-2-Dimethylphosphonoformamido-5-hydroxy-pent-3-enoic acid, δ-lactone (74). m/z: 217 (M-MeOH) and 205 ($M-CO_2$).

Peak Four (Scan #202) N-Methyl 2-dimethylphosphonoformamido-5-hydroxy-pent-2-enoic acid, δ-lactone (75). m/z: 233 ($M-CH_2O$).

Peak Five (Scan #292) Methyl (Z)-(2R)-5-dimethylphosphono-2-methylcarbamoyl-pent-3-enoate (68) - previously characterised.

Attempted formation of methyl (Z)-(2R)-5-dimethylphosphono-2-methylcarbamoyl-pent-3-enoate (68) by alkali-metal salt catalysed Arbusov lactone cleavage

A solution of the lactone (61) in trimethylphosphite containing a little CsF (or LiBr) was heated to reflux but no appreciable improvement in reaction was observed by gc-analysis, starting material only slowly being converted to product isomers (68).

Attempted formation of (Z)-(2R)-5-dimethylphosphono-2-methyl-carbamoyl-pent-3-enoic acid (76) by acid catalysed Arbusov reaction

A solution of the lactone (61) in trimethylphosphite containing a catalytic quantity of H_2SO_4 was maintained at elevated temperature (90-100°C) for ca. 5 days. Then, gc-analysis of the reaction mixture revealed formation of several materials and

tentative structures assigned on the basis of their gc-ms spectra. (Run conditions: 100-280°C, 15° per minute).

Peak One (Scan #141) N-Methyl 3-methylcarbamoyl pyran-2-one (77). m/z: 183 (M) and 152 (M-OMe).

Peak Two (Scan #148) Major, unidentified product. m/z: 171, 156, 139, 128 and 112.

Peak Three (Scan #153) N-Methyl (2R)-5-hydroxy-2-methyl-carbamoyl-pent-3-enoic acid, δ-lactone (73). m/z: 185 (M), 170 ($M-CH_3$), 153 (M-MeOH) and 126 ($M-CH_3-CO_2$).

Peak Four (Scan #172) 5-Hydroxy-2-methylcarbamoyl-pent-2-enoic acid, δ-lactone (62). m/z: 171 ([M+1]), 139 (-MeOH) and 109 ([139] $-CH_2O$).

Reaction of lactone (61) with sodium dimethylphosphite: Attempted formation of (Z)-(2R)-5-dimethylphosphono-2-methylcarbamoyl-pent-3-enoic acid (76)

Hot, oven-dried glassware was charged with sodium hydride (12 mg, 0.5 mmol) and blown cold with dry nitrogen. This was then suspended in freshly-distilled THF (5 ml), dimethylphosphite (0.12 ml, 1.3 mmol) added and the anionic nucleophile formed by heating at reflux for ca. 5 minutes. Then a solution of the lactone (61) (75 mg, 0.44 mmol) in THF (2 ml) was added and the mixture refluxed for 2-3 hours when gc-analysis revealed consumption of starting material. The product was recovered by evaporation of the THF in vacuo and re-solution in distilled H_2O. This aqueous solution was back-washed with three volumes of DCM and then lyophilised to give an off-white semisolid (71.8 mg). This material

has not proved to be identifiable, but may be a product of O-acyl lactone cleavage; δ_H (D_2O) 7.83 (1H, b), 6.77 (1H, dt, J 10.5, 6.5 Hz, =CH), 6.1 (1H, br d, J 10.8 Hz, =CH), 5.47 (1H, s), 5.27 (1H, dd, J 16.1, 2 Hz, 5-H), 5.14 (1H, dd, J 16.2, 2 Hz, 5-H), 3.67 (3H, s, -OMe), 3.6-3.5 (4H, d, J 11 Hz, -POMe); δ_C (D_2O) 171.7, 156.4 (each, C=O), 133.7 (minor, =CH), 132.6 (=CH), 119.3 (minor, =CH), 118.6 (=CH), 77.2, 58.4, 52.7, 50.8, 50.7, 38.7, 18.4; δ_p (D_2O) 8.3.

KF-Al_2O_3 mediated reaction of lactone (61) with dimethylphosphite - Attempted formation of (Z)-(2R)-5-dimethylphosphono-2-methyl-carbamoyl-pent-3-enoic acid (76)

A solution, in THF, of the lactone (61) (89.3 mg, 0.52 mmol) and dimethylphosphite (0.053 ml, 0.52 mmol) was adsorbed onto KF on alumina (0.4 g) and heated at 80°C for two hours, then left overnight at room temperature. The organic products were then desorbed by washing the solids with organic solvents. Ethyl acetate extraction produced a mixture of conjugated lactonic material (62) and, possibly N-methylated material (73) (21.5 mg) δ_H ($^2H_4$MeOH) 7.54 (1H, br, NH), 7.18 (1H, t, J 4.4 Hz, 3-H), 4.44 (2H, t, J 6.6 Hz, 5 -H and 5 -H), 3.73 (3H, s, -OMe), 3.12 (1.5 H, s, NMe) and 2.59 (2H, td, J 6.6, 4.4 Hz, 4-H); m/z: (E.I.) 185 (M for (73)), 171 (M for (62)), 139 (M for (62) -MeOH).

Reaction of lactone (49) with trimethylsilyliodide - Attempted formation of trimethylsilyl (Z)-(2R)-5-iodo-2-(2',2',2'-trichloro-acetamido)-pent-3-enoate (80)

To a solution of the lactone (49) (11 mg, 0.4 mmol) in acetonitrile (1 ml) containing sodium iodide (32 mg, 0.2 mmol) was added trimethylsilylchloride (0.027 ml, 0.2 mmol) and the mixture heated at reflux for an extended period, whilst protected from light. (The solution darkened markedly). After 24 hours, further portions of sodium iodide and trimethylsilylchloride were added and the mixture heated for a further two days when products were recovered by dissolving the reaction mixture in ether (40 ml) and washing with brine containing sodium thiosulphate (2 x 10 ml). The residue (7.7 mg) on drying ($MgSO_4$) and concentration, was analysed by gc-ms. (Run conditions: 100-280°C, 15°C per minute). Only tentative structural assignments could be made from the spectral data. Starting material (49) was recovered and the other major component appeared to be 3-(2',2',2'-trichloroacetamido)-pyran-2-one (59), m/z: 255 (M), 220 (M-Cl) and 139 ($M-CCl_3$).

Ethyl (Z)-(2R)-5-bromo-2-(2',2',2'-trichloroacetamido)-pent-3-enoate (82)

A solution of the lactone (49) (20 mg, 0.07 mmol) in absolute EtOH (2 ml) was chilled in an ice-bath, then HBr added *via* a bubbler (generated from the reaction of tetralin and Br_2). The resulting solution was stirred overnight at room temperature then the complex mixture of products recovered by pouring the reaction mixture into one volume of brine and the combined soution extracted

with five volumes of ether. The ether extracts were combined and back-washed with brine, then dried ($MgSO_4$). Separation of this complex mixture by chromatography (eluant: ethyl acetate - petrol) was attempted but not all the fractions obtained could be analysed. The most mobile material recovered was tentatively assigned as **ethyl 2-(2',2',2'-trichloroacetamido)-penta-2,4-dienoate** (83) (5.1 mg, 28%), ν_{max} (CH_2Cl_2) 3350 (NH) and 1710 cm^{-1} (C=O), δ_H ($CDCl_3$) 9.1 (1H, br, NH), 7.88 (1H, d, J 11.3 Hz), 7.4 (1H, m), 5.65 (1H, m), 5.53 (1H, m), 4.4 (2H, q, J 7.1 Hz, $-O\underline{CH_2}CH_3$) and 1.42 (3H, t, J 7.1 Hz, $-OCH_2\underline{CH_3}$); m/z: (C.I.) 286 [M+1] and 240 ([M+1] -EtOH) and a slightly more polar material was tenatively assigned as the desired **ethyl (Z)-(2R)-5-bromo-2-(2',2',2'-trichloroacetamido)-pent-3-enoate** (82) (8.2 mg, 29%), ν_{max} (CH_2Cl_2) 3390 (NH) and 1710 cm^{-1} (C=O); δ_H $CDCl_3$) 7.5 (1H, b, NH), 6.1 (1H, dt, J 15, 7.7 Hz, 4-H), 5.4 (1H, m, 2-H), 5.25 (1H, m, 3-H), 4.3 (3H, m, 5-H and $-O\underline{CH_2}CH_3$), 4.1 (1H, m, 5-H) and 1.33 (3H, t, J 7.14 Hz, $-OCH_2\underline{CH_3}$); m/z: (C.I.) 366 (M+1), 320 ([M+1] -EtOH), 292 ([M+1] -HCOOEt) and 286 ([M+1] -HBr).

Attempted transition metal catalysed ring opening of lactone (61)

To a solution of the lactone (61) in triethylphosphite was added a catalytic quantity of $PdCl_2$. The solution initially adopted a yellow colouration which faded over a period of one day at room temperature, when gc-analysis revealed the formation of a less volatile material and remaining lactone. GC-MS analysis (Run conditions: 100-280°C, 15° per minute) of this mixture suggested that the lactone had undergone metal-assisted conjugation and

subsequent Michael addition. Possible structural assignments were as follows:-

Peak One (Scan #176) 5-Hydroxy-2-methylcarbamoyl-pent-2-enoic acid,δ-lactone (62). m/z: 171 (M), 139 (M-MeOH) and 109 (139 $-CH_2O$).

Peak Two (Scan #202) 3-Diethylphosphono-5-hydroxy-2-methyl-carbamoyl-pentanoic acid, δ-lactone (84). m/z: 263 (M-EtOH) and 235 (M-NHCOOMe).

Attempted formation of methyl (Z)-(2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enoate (85) by methanolysis

A solution of the lactone (61) was refluxed in methanol under a $CaCl_2$-guard tube for an extended period (ca. 2 days) but no reaction was seen by tlc/gc-analysis.

Attempted formation of methyl (Z)-(2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enoate (85) by acid-catalysed methanolysis

A solution of the lactone (61) in methanol containing Amberlyst 15 acid resin was stirred at room temperature overnight. An equilibrium seemed to be established and the new material possibly was the hydroxy methyl ester (85) by gc-ms analysis. (Run conditions: 100-280°C, 15° per minute). m/z: 185 ($M-H_2O$), 153 (M-MeOH) 144 (M-COOMe).

Acid-catalysed methanolysis of lactone (61) - Attempted formation of methyl (Z)-(2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enoate (85)

A solution of the lactone (61) (77 mg, 0.45 mmol) in methanol (2 ml) containing a little Amberlyst 15 H^+ resin was refluxed for several hours. TLC analysis revealed partial reaction to two more mobile materials which were recovered by filtration of the resin and evaporation of the solvent. Column chromatography (eluant: 10% ethyl acetate in petrol) effected separation of two unidentified products from remaining starting material (40.3 mg) but only partially separated the two. Early fractions contained a colourless solid (1.2 mg), ν_{max} (CH_2Cl_2) 3410 (NH) and 1710 cm^{-1} (C=O); δ_H ($CDCl_3$) 5.8 (1H, m, =CH), 5.6 (1H, m, =CH), 5.0 (1H, b), 4.76 (1H, d, J 4.2 Hz, NH), 4.5 (1H, m, 2-H), 4.1 (2H, m, 5α-H and 5β-H), 3.68 (3H, s, -OMe) and 3.47 (3H, s, -OMe); m/z (C.I.) 196, 188, 170, 156 and 127. Then, some mixed fractions were eluted (6.4 mg), followed by fractions containing colourless crystalline material (7.3 mg), m.p. 55°C, ν_{max} (CH_2Cl_2) 3410 (NH) and 1710 cm^{-1} (C=O); δ_H ($CDCl_3$) 5.95 (1H, m, =CH), 5.8 (1H, m, =CH), 4.8 (1H, b), 4.68 (1H, br), 4.18 (1H, m, 5-H), 4.15-4.05 (2H, m, 2-H and 5-H), 3.68 (3H, s, -OMe) and 3.48 (3H, s, -OMe); m/z: (C.I.) 196, 186, 170, 156 and 127.

Base-catalysed methanolysis of the lactone (61) - Attempted formation of methyl (Z)-(2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enoate (85)

To a solution of the lactone (61) (33.5 mg, 0.2 mmol) in methanol (2 ml) equilibrated in an ice-bath was added a catalytic

quantity of K_2CO_3. TLC analysis after having allowed the reaction mixture to warm to room temperature showed almost complete consumption of starting mateial to two materials; one more polar, one less polar than the starting lactone. The less polar material was again the conjugated lactone (62) (12.8 mg, 41.3% based on recovered starting material) and the more polar material (7.4 mg, 20.1% based on recovered starting material) appeared to contain a mixture of alcohols which were not separated further, m/z (C.I.) 204 ([M+1]) and 172 ([M+1]-MeOH).

Reaction of lactone (61) with piperidine - Trial Scale

A solution of the lactone (61) in THF containing a little piperidine was refluxed for 6-8 hours when gc-ms analysis (Run conditions: 100-280°C, 15° per minute), of the reaction mixture revealed the presence of conjugated lactone (62) and a less volatile material (Scan #286) which was perhaps piperidinyl (Z)-(2R)-5-hydroxy-2-methylcarbamoyl-pent-3-enamide (86), m/z: 144 (M-CO piperidinyl), 112 (CO piperidine) and 58 ($HOCH_2CH=CH_2$).

Attempted trapping of the acyclic isomer of the 2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranoses (45) by acetylation

A solution of the lactol (45) (66.3 mg, 0.25 mmol) in dry DCM (3 ml) containing pyridine (excess) and acetic anhydride (0.036 ml, 0.75 mmol) was foil-wrapped and stored in a refrigerator for four days. TLC analysis then showed complete reaction to a more mobile material which was recovered by washing with two volumes of 2 N

HCl, one volume of saturated aqueous $CuSO_4$, two volumes of saturated aqueous $NaHCO_3$ and one volume of water, then drying the organic solution ($MgSO_4$). Column chromatography gave the ring acetate product (87) (65 mg, 84.8%) as an anomeric mixture; ν_{max} (CH_2Cl_2) 3420 (NH), 1750 (acetyl C=O) and 1710 cm^{-1} (amide C=O); δ_H ($CDCl_3$) 6.8 (1H, br, NH), 6.1 (2H, m, =CH and 1-H), 5.8 (1H, m, =CH), 4.75-4.3 (3H, m, 5 -H, 5 -H and 2-H) and 2.15-2.10 (3H, two s, each $-COCH_3$); δ_C ($CDCl_3$) 169.1 (C=O), 130.4, 129.7, 121.7, 119.8 (each, =CH), 90.9, 89.7 (each, 1-C), 62.9, 60.4 (each, 5-C), 46.3, 46.1 (each, 2-C) and 20.8 ($-COCH_3$); m/z: (C.I.) 242 ([M+1] $-COOCH_3$) and 213 ([M+1] -HCOOAc).

Attempted trapping of the acyclic isomer of the 2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranoses (45) by formation of a hydrazone

The lactol (45) (81.3 mg, 0.31 mmol) was dissolved in a 3:1 mixture of hot H_2O : EtOH (4 ml) and this solution allowed to cool to room temperature.

Similarly, phenylhydrazine hydrochloride (0.05 g, 0.34 mmol) and sodium acetate (0.056 g, 0.68 mmol) were dissolved in hot distilled water (6 ml) and allowed to cool to just above room temperature when the lactol solution was added. The resulting clear solution became slowly cloudy and this suspension settled overnight. The products were recovered by decanting off the supernatant from the settled solids and the residues dissolved in ethyl acetate and dried ($MgSO_4$). The residue on filtration and evaporation was purified by chromatography (eluant: ethyl acetate

in petrol) to give material suspected to be the hydrazinoglycoside (88) (34.5 mg, 31.7%), ν_{max} (CH_2Cl_2) 3490 (NH) and 1700 cm^{-1} (C=O); m/z: (C.I.) 350 ([M+1]), 314 ([M+1] -HCl) and 242 ([M+1] -NHNHPh).

Reaction of the 2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranoses (45) with ethanethiol

To a solution of lactol (45) (72 mg), 0.28 mmol) in ethanethiol (3 ml) was added 1 drop of concentrated HCl. The reaction mixture was kept for 1 day in the refrigerator but tlc analysis showed only the presence of starting material. A further day at room temperature caused complete conversion to a less polar material by tlc. The product was recovered by evaporation of the thiol in vacuo, column chromatography of the residue (eluant: 10% ethyl acetate in petrol) gave the ethyl 2,3,4-trideoxy-1-thio-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranosides (89) (51.4 mg, 61%) as an anomeric mixture; ν_{max} (CH_2Cl_2) 3400 (NH) and 1700 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.9 (1H, b, NH), 6.1-5.9 (2H, m, 3-H and 4-H), 5.14 (1H, s, 1-H), 4.5-4.45 (1H, m, 5-H), 4.35 (1H, m, 2-H), 4.2-4.1 (1H, dt, J 17.9, 2.6 Hz, 5-H), 2.8-2.6 (2H, m, $-S\underline{CH_2}CH_3$) and 1.32 (3H, t, J 7.5 Hz, $-SCH_2\underline{CH_3}$); δ_C ($CDCl_3$) 161.1 (C=O), 131.3, 120.8 (each, =CH), 82.3 (1-C), 59.2 (5-C) 48.3 (2-C), 25.4 ($-S\underline{CH_2}CH_3$) and 15.1 ($-SCH_2\underline{CH_3}$); m/z: (E.I.) 213 ($M-HCOSCH_2CH_3$), (C.I.) 304[M+1], 286 ([M+1]$-H_2O$) and 242 ([M+1] -HSEt).

Reaction of the 2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-D-glycero-pent-3-enopyranoses (45) with propanedithiol

To a solution of the lactol (45) (0.21 g, 0.81 mmol) in dry DCM (5 ml) containing propanedithiol (0.1 ml, 0.97 mmol) was added a catalytic quantity of BF_3.etherate (0.01 ml, 0.08 mmol) and the mixture stirred at room temperature for ca. 2 days. TLC analysis then showed complete conversion of starting material to two more mobile materials which were separated by chromatography (eluant: ethyl acetate in petrol) to give the anomeric 3'-mercaptopropyl 2,3,4-trideoxy-1-thio-2-(2",2",2"-trichloroacetamido)-D-glycero-pent-3-enopyranosides (90) as a clear oil (159 mg, 56.3%), ν_{max} (CH_2Cl_2) 3400 (NH) and 1700 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.9 (1H, br, NH), 6.1-6.0 (1H, m, =CH), 5.9-5.8 (1H, m, =CH), 5.1 (1H, s, 1-H), 4.55-4.4 (1H, m, 5-H), 4.4-4.3 (1H, m, 2-H), 4.2-4.1 (1H, m, 5-H), 2.8-2.6 (2H, td, J 1.0, 4.4 Hz); 2.8-2.6 (2H, dd), 2.0 (2H, dd) and 1.4 (1H, t, J 8 Hz, SH). δ_C ($CDCl_3$) 161.1 (C=O), 131.3, 120.7 (each, 3-C and 4-C), 92 ($-CCl_3$), 82.5 (1-C), 59.4 (5-C), 48.3 (2-C), 35.5 (CH_2), 29.5 (CH_2) and 23.4 (CH_2); m/z: (E.I.) 242 ($M-SCH_2CH_2CH_2SH$), 213 ($M-HCOSCH_2CH_2CH_2SH$), (C.I.) 350 [M+1] and the more polar 1,3-[2',3',4'-trideoxy-1'-thio-2'-(2",2",2"-trichloroacetamido)-D-glycero-pent-3-enopyranosidyl] propanes (91) as an anomeric mixture (75.4 mg, 26.7%), ν_{max} (CH_2Cl_2) 3400 (NH) and 1705 cm^{-1} (C=O), δ_H ($CDCl_3$) 6.9 (2H, b, NH and NH'), 6.1-6.0 (2H, m, =CH and =CH'), 5.9-5.8 (2H, m, =CH and =CH'), 4.9-4.8 (2H, b, 1-H and 1-H'), 4.55-4.45 (2H, m, 5-H and 5-H'), 4.4-4.3 (2H, m, 2-H and 2-H'), 4.25-4.15 (2H, m, 5-H and 5-H'), 2.8 (4H, dd, J 13.0, 7.1 Hz, each $-SCH_2$) and 2.0 (2H, m, $-SCH_2CH_2CH_2S-$); δ_C ($CDCl_3$) 161.2 (2

x C=O), 131.3, 120.8 (each, 2 x CH), 92.2 (2 x $-CCl_3$), 82.5 (2 x 1-C), 59.5 (2 x 5-C), 48.3 (2 x 2-C) and 29.9, 29.8 (each CH_2); m/z: (E.I.) 242 ($M-SCH_2CH_2CH_2R$) and 213 ($M-HCOSCH_2CH_2CH_2R$).

Iodo-cyclisation of the trichloroacetamidate (8a)

To a solution of the trichloroimidate (8a) (0.425 g, 1.55 mmol) in dry dichloromethane (10 ml) was added N-iodosuccinimide (0.376 g, 1.67 mmol) and the mixture stirred under nitrogen, wrapped in foil, until tlc showed complete reaction (10 days at room temperature). The pink reaction mixture was washed with aqueous sodium thiosulphate (1 volume), water, dried ($MgSO_4$) and evaporated in vacuo, when chromatographic purification (eluant: ethyl acetate - petrol) gave the desired iodo-cyclised product, **methyl 2-iodo-2,3-dideoxy-4,3-(2'-trichloromethyl-1'-oxa-3'-azaprop-2'-eno)-β-D-arabino-pentopyranoside** (24), in good yield (0.58 g, 94%), m.p. 113-115°C (Found: C, 24.0; H, 2.2; N, 4.2; $C_8H_9NO_3Cl_3I$ requires C, 24.0; H, 2.3; N, 3.5); ν_{max} (CH_2Cl_2) 1640 (C=N); δ_H ($CDCl_3$) 4.84-4.7 (3H, m, 1-H, 3-H and 4-H), 4.29 (1H, dd J 13.2, 4.4 Hz, 5-H), 4.04 (1H, dd, J 13.2, 4.7 Hz, 5-H), 3.80 (1H, dd J 7.7, 7.0 Hz, 2-H) and 3.48 (3H, s, -OMe); δ_C ($CDCl_3$) 163.9 (C=N), 103.1 (1-C), 79.3 (2-C), 76.5 (3-C), 71.7 (4-C), 60.7 (5-C) and 56.6 (-OMe); m/z: (E.I.) 399 (M), 368 (M-OMe), 296, 272 (M-I), (C.I.) 400 ([M+1]), 368 ([M+1]-HOMe) and 272 ([M+1] -HI).

Hydrolysis of the oxazoline (24) to a 3-amino xylose derivative - A preliminary investigation

A solution of the oxazoline (24) (0.53 g, 1.32 mmol) in

methanol (5 ml) containing H_2O (0.44 ml) was refluxed for 24 hours, after which time tlc analysis revealed complete consumption of starting material. The solvent was then removed under reduced pressure and the residue purified chromatographically (eluant: 40% ethyl acetate in petrol). However, a quantity of starting material (0.19 g) was recovered as well as two less mobile materials, the first eluted of which appearing to be the methyl 2,3-dideoxy-2-iodo-3-(2',2',2'-trichloroacetamido)-α-L-xylo-pentopyranoside (25) (0.22 g, 63% based on recovered starting material), ν_{max} (CH_2Cl_2) 3600 (OH), 3400 (NH), 1710 (C=O) and 800 cm^{-1} (C-I); δ_H ($CDCl_3$) 7.4 (1H, br, NH), 5.0 (1H, d, J 3 Hz, 1-H), 4.5 (2H, m), 4.0 (3H, m, 5α-H, 5β-H and CH), 3.6 (3H, s, -OMe) and 3.2 (1H, b, -OH); m/z: (E.I.) 385 (M-MeOH), 296, 272 (M-$COCCl_3$), (C.I.) 418 ([M+1]), 400 ([M+1]-H_2O) and 386 ([M+1]-MeOH).

Epoxidations of the methyl 2,3,4-trideoxy-2-(2',2',2'-trichloroacetamido)-β-D-*glycero*-pent-3- enopyranoside (9b) and of the methyl 2,3,4-trideoxy-2-methylcarbamoyl-β-D-*glycero*-pent-3-enopyranoside (40b) were performed under the supervision of R J Ogilvie by project students.[214]

Epoxidation of the (2*R*)-5-hydroxy-2-methylcarbamoyl-pent-3-enoic acid,δ-lactone (61)

To a solution of the lactone (61) (0.10 g, 0.58 mmol) in dried $CHCl_3$ (10 ml) was added *m*CPBA (0.40 g, 2.9 mmol) and the resultant solution stirred at room temperature for *ca*. 3 days when gc-analysis showed complete consumption of starting material.

Attempting to recover the products by washing the reaction mixture successively with aqueous sodium thiosulphate solution, saturated sodium bicarbonate solution and saturated brine was unsuccessful, only mCPBA being recovered. The aqueous solutions were therefore saturated with NaCl and re-extracted with ethyl acetate (6 x 1 volume) and dried ($MgSO_4$). Concentration and chromatography (eluant: ethyl acetate in petrol) gave a white waxy solid (35.7 mg) which was still contaminated with mCPBA, but appeared to contain a mixture of stereoisomers as shown by nmr analysis (2 x -OMe singlets). m/z: (E.I.) 187 (M), 156 (M-MeO), 128 (M-COOMe).

Preliminary studies of epoxide ring opening of (92) with sodium azide

A solution of the epoxide (93) (42.0 mg, 0.14 mmol) in dry DMF (10 ml) was treated with sodium azide (47 mg, 0.7 mmol) and heated at reflux for ca. 8 hours when tlc analysis revealed complete reaction to a more polar material. This was recovered by evaporation of the solvent and chromatography (eluant: ethyl acetate) giving an azide (94) (18.8 mg, 39%) as an oil. ν_{max} (CH_2Cl_2) 3600 (OH), 3430 (NH), 2100 (N_3) and 1770 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.01 (1H, b), 4.58 (2H, m), 3.8 (4H, m), 3.43 (3H, s, -OMe) and 1.25 (1H); δ_C ($CDCl_3$) 159.0 (C=O), 99.6 (1-C), 77 (CH), 59.1 (5-C), 57.2 (CH), 55.9 ($-OCH_3$) and 54.4 (CH); m/z: (E.I.) ($M-OH-NHCOCCl_3$), (C.I.) 260, 256, 228, 215 and 154.

Attempted glycosidic hydrolysis of methyl 3,4-anhydro-2-deoxy-2-methylcarbamoyl-β-D-pentopyranoside (93)

To a solution of the epoxidised glycoside (93) (50.8 mg, 0.25 mmol) in a mixture of distilled water (5 ml) and THF (2 ml) was added 2 M HCl solution (2 ml) and the mixture stirred at room temperature for ca. 3 days when complete conversion of starting material was observed by gc-analysis. The products were recovered by neutralisation (aq. NaOH) and lyophilisation and the residues extracted with ethyl acetate (4 x 10 ml). These extracts were combined, dried, filtered and evaporated (leaving 50.9 mg) and the residue separated by column chromatography giving an unidentified mobile material (20 mg), ν_{max} (CH_2Cl_2) 3580 (OH), 3410 (NH) and 1720 cm^{-1} (C=O); δ_H ($CDCl_3$) 5.14 (1H, d, J 7.7 Hz), 4.71 (1H, d, J 1.65 Hz), 4.2-4.0 (2H, m), 3.8 (2H, m), 3.7 (3H, s, -OMe), 3.39 (3H, s, -OMe), 2.0 (1H, br, -OH, exch.) and 1.26 (2H, m); δ_C ($CDCl_3$) 100.4 (1-C), 70.4 (CH), 62.1 (5-C), 56.5, 55.4 and 54.5 (each, CH); m/z: (E.I.) 208, 190, 161, 149, 131, 117 and 112 and a polar component (95) (5 mg, 9%) tentatively identified as a product of epoxide hydrolysis, ν_{max} (CH_2Cl_2) 3590 (OH) 3430 (NH) and 1715 cm^{-1} (C=O); δ_H (400 MHz, $CDCl_3$) 5.24 (1H, br d, NH), 4.61 (1H, d, J 1.8 Hz), 4.08 (1H, br), 3.96 (1H, m), 3.8-3.7 (2H, m), 3.70 (3H, s, -OMe), 3.50 (2H, m), 3.38 (3H, s, -OMe) and 3.25 (1H, br) m/z: (C.I.) 222 ([M+1]), 204 ([M=1] $-H_2O$), 190 ([M+1] -MeOH), 172 204 $-H_2O$) and 158 ([190] -MeOH).

Attempted glycosidic hydrolysis of methyl 3,4-anhydro-2-deoxy-2-(2',2',2'-trichloroacetamido)-β-D-pentopyranoside (92)

To a solution of the epoxidised glycoside (92) (86 mg, 0.3 mmol) in a mixture of distilled water (5 ml) and THF (2 ml) was added a little 2 M HCl solution (2 ml) and the mixture stirred at room temperature for 2 days when complete conversion of starting material was observed by gc-analysis. The products were recovered by neutralisation (aq. NaOH), saturation of the solution with NaCl and extracting exhaustively with $CHCl_3$ (6 volumes). These extracts were combined, dried ($MgSO_4$) and concentrated (leaving 72.5 mg) and the residue separated into its components by column chromatography giving an unidentified mobile material (43.2 mg), ν_{max} (CH_2Cl_2) 3575 (OH), 3405 (NH) and 1720 cm^{-1} (C=O); δ_H ($CDCl_3$) 6.88 (1H, br d), 4.81 (1H, d, $\underline{J}$ 2.4 Hz), 4.37 (1H, m, 5-H), 4.21 (1H, dd, $\underline{J}$ 8.8, 3.85 Hz, 5-H), 3.74 (3H, s, -OMe) and 2.88 (1H, b, -OH, exch.); δ_C ($CDCl_3$) 162.7 (C=O), 99.3 (1-C), 70.1 (CH), 62.0 (5-H), 56.2 (CH), 55.7 (-OMe) and 54.3 (CH); m/z (E.I.) 276, 230 (C.I.) 326, 294, 276 and 268 and a polar component (95) (10.1 mg, 11%) tentatively identified as a product of epoxide hydrolysis, ν_{max} (CH_2Cl_2) 3590 (OH), 3420 (NH) and 1715 cm^{-1} (C=O), δ_H ($CDCl_3$) 6.99 (1H, d, $\underline{J}$ 8.4 Hz), 4.89 (1H, d, $\underline{J}$ 3.3 Hz), 4.5-4.0 (3H, m), 4.0-3.5 (3-4H, m) and 3.49-3.39 (3H, s); m/z: (C.I.) 308 ([M+1]), 276 ([M+1]-MeOH) and 258 ([276]-H_2O).

Cis-hydroxylation of lactone (61) with osmium tetroxide - A preliminary investigation into the formation of the polyhydroxylated amino acid, δ-lactone (97)

Osmium tetroxide (100 mg, 0.4 mmol) in freshly-distilled THF (1 ml) was added to a solution of the unsaturated lactone (61) (67.2 mg, 0.39 mmol) in THF (2 ml) at room temperature. This addition caused the solution to blacken. GC-analysis showed complete consumption of starting material after 10 hours. Treating the reaction mixture with H_2S for one hour and stirring the saturated solution overnight gave a white froth (77.5 mg, 96%) on filtration and concentration in vacuo, which possibly was the desired diol (97), ν_{max} (CH_2Cl_2) 3400 (OH and NH), 1750 (C=O) and 1720 cm^{-1} (C=O), δ_H ($CDCl_3$ + $^2H_6$ DMSO) 6.53 (1H, d, J 8.4 Hz), 5.41 (1H, d), 5.02 (1H, m), 4.45 (1H, dd, J 8.8, 2.75 Hz), 4.3 (2H, m), 4.2 (2H, m), 3.69 (3H, s, -OMe) and 3.5 (1H, b); δ_H (D_2O) 4.62 (1H, t, J 3.6 Hz), 4.49 (1H, d, J 5.8 hz), 3.9-3.8 (2H, m, 5 -H and 5 -H) and 3.7 (3H, s, -OMe); δ_C ($^2H_6$DMSO) 169.9 (C=O), 156.8 (C=O), 69.5 (CH), 69.4 (5-C), 64.8 (CH), 54.5 (-OMe) and 52.2 (CH); m/z: (C.I.) 206 ([M+1]), 188 ([M+1] $-H_2O$), 174 ([M+1]-MeOH) and 170 ([188] $-H_2O$).

Cis-hydroxylation of the unsturated glycoside (9b) with osmium tetroxide - A preliminary investigation into the formation of methyl 2-deoxy 2-(2',2',2'-trichloroacetamido)-pentanopyranoside (98)

Osmium tetroxide (67 mg, 0.26 mmol) in freshly-distilled THF (1 ml) was added to a solution of the unsaturated glycoside (9b)

(66.1 mg, 0.24 mmol) in THF (4 ml) at room temperature. The addition caused a moderately rapid discolouration. GC-analysis revealed complete conversion of starting material after two days and the products recovered by treating the reaction mixture with H_2S for 1 hour, stirring the saturated solution overnight, filtration and concentration in vacuo as an off-white oil (74.6 mg, 10%), ν_{max} (CH_2Cl_2) 3500 (OH), 3400 (NH) and 1700 cm^{-1} (C=O); δ_H ($CDCl_3$ + $^2H_6$DMSO) 8.19 (1H, d, J 7.9 Hz), 4.43 (1H, d, J 7.33 Hz), 4.0-3.8 (8H, m) and 3.44-3.37 (3H, two s, each -OMe); δ_H (D_2O added) 8.00 (1H, d), 4.70 (2H, b), 4.48 (1H, d, J 6.4 Hz), 4.0-3.8 (6H, m) and 3.46-3.38 (3H, two s, each -OMe); δ_C ($CDCl_3$ + $^2H_6$DMSO) 162.3 (C=O), 101.9 (99.7) (1-C), 93.15 (CCl_3), 70.0 (68.6) (CH), 67.9 (63.0) (CH), 65.9 (63.2) (5-C), 56.3 (55.0) (-OMe) and 55.1 (54.1) (CH); m/z (C.I.) 308 ([M+1]), 276 ([M+1] -MeOH) and 258 ([276] $-H_2O$). This mixture was not purified further and the components of the mixture remain unidentified.

APPENDIX ONE

The Peptide Transport System:-[123]

Since there are relatively few biologically-significant amino acids, it is perfectly within reason for the cell to possess a specific transport facility for either individual amino acids or structurally-related types.

However the vast number of peptide structures (~400 dipeptides, ~8000 tripeptides etc.) makes the existence of an individual transport system for each highly impractical.

A priori, therefore, it seems that the ideal way to ensure peptide transport resides in designing a minimum number of systems that possess requirements for only those unique structural features common to all oligopeptides.

The characteristics of peptide transport have been probed, elegantly, using genetically deficient cell-lines, amino acid auxotrophs and functionalised oligopeptides in growth studies. In this way the absolute requirements of peptide transport are being established.

For instance, to discover the essential or non-essential nature of the free terminal α-amino group for peptide uptake, *N*-acetyl-di- and tetrapeptides were fed and were nutritionally inactive (though not inhibitory) whereas *N*-acetyl tripeptides permitted only very slow growth. This failure to support growth must therefore result from a defect in transport or hydrolysis. Further to this, using whole-cell and lysed-cell studies, it has been shown that the cells possessed the enzymatic machinery for hydrolysing *N*-α-acetyl peptides and that the nutritional ineffectiveness of the peptide must derive from its

inability to enter the cell.

Stated formally, the presence of an α-unsubstituted α-amino group in a peptide appears to be generally essential for peptide uptake, but the reason for this remains undefined. Is it due to the loss of charge / Schiff base formation ability or is it simply due to steric effects?

Similarly the role of the *C* -terminal carboxy-group in peptide transport has been investigated and decarboxylated C-terminal oligopeptides have been shown to be transported readily on the same oligopeptide transport system as genuine peptidic material, though this alteration may reduce the specific affinity in competitive studies.

Interestingly, the autonomous dipeptide transport system has an absolute requirement for both terminal amine and carboxylate functionality.

Also, there seems to be a size restriction on peptide transport - longer peptidic units (≧5) are *not* transported (are fed but are not nutritious), suggesting a basic requirement of a limit on hydrodynamic volume, dependent on charge per unit volume, solvation and conformation.

Peptide transport has been shown to be energy-dependent, actively transported rather than reliant upon the forces of diffusion. This was elucidated when inhibitors of energy-coupling were shown to prevent peptide accumulation.

All this leads to the conclusion that phosphonated amino acids are unlikely to be transported as free units by specific transporters but are much more accessible when incorporated in di- or tri-peptides. It would also suggest that any tripeptide unit containing the 'warhead' aminophosphonic acid ought to be similarly active.

Appendix Two:- Biosynthesis of Phosphonates

The natural occurrence of phosphonate materials, such as the amino phosphonic acid constituent of plumbemycin, necessitates that there be a mechanism for the formation of the *P-C* bond from non-phosphonate precursors.

There are two main pathways which have been advanced to explain the biogenesis of phosphonates. These involve the rearrangement of phosphoenol pyruvate (or a reduced phosphino-variant) (See Figure 208).

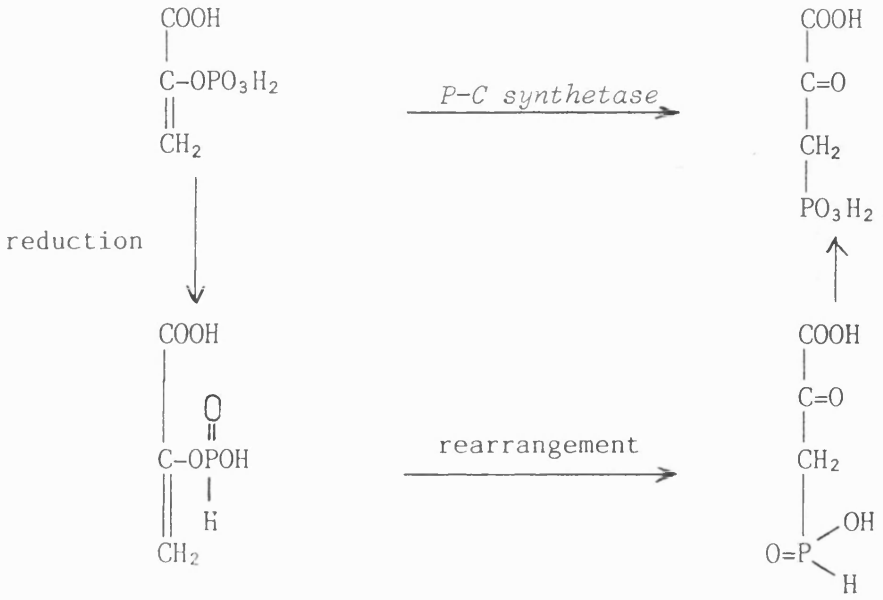


Figure 208

(The enzymes responsible for such processes remain undiscovered.)

These rearrangements, and subsequent biochemical manipulation, are enough to account for most of the known natural phosphonates. An exception is the tyrosine phosophono-analogue; this might, however, be readily rationalised as an addition of orthophosphite to *p*-hydroxy-phenylacetaldehyde, followed by oxidation and transamination (see Figure 209).

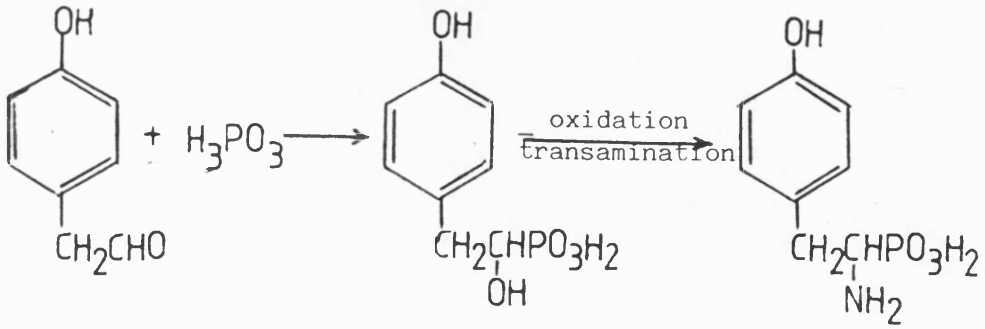


Figure 209

So where does this leave an evaluation of the biosynthesis of the APPA constituent from the Plumbemycins?

Essentially two possible mechanisms can be envisaged. The first involves a rearrangement of phosphoenol pyruvate, followed by decarboxylation and condensation of the resulting aldehyde with further phosphoenol pyruvate. Finally, transamination gives the desired aminophosphonic acid material, through the geometry of the double bond must be suspect (see Figure 210).

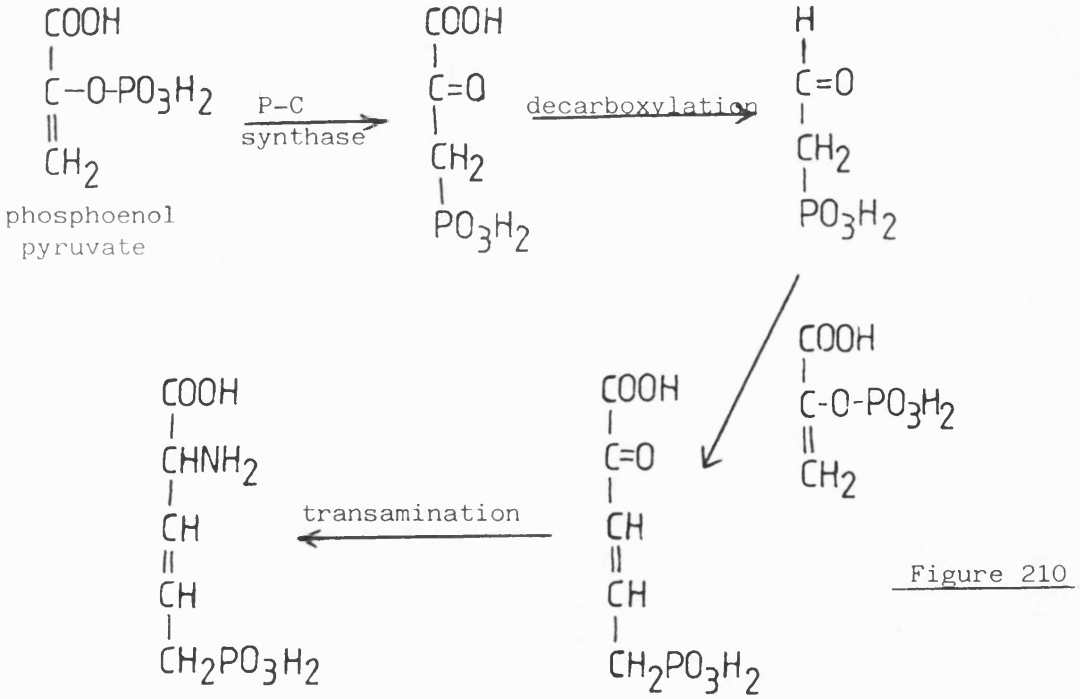


Figure 210

The second mechanism provides a means of constraining the double bond geometry as *cis*- by invoking a vinylogous extension of the phosphoenol-phosphonate rearrangement, proceeding *via* a small

ring transition state. (see Figure211).

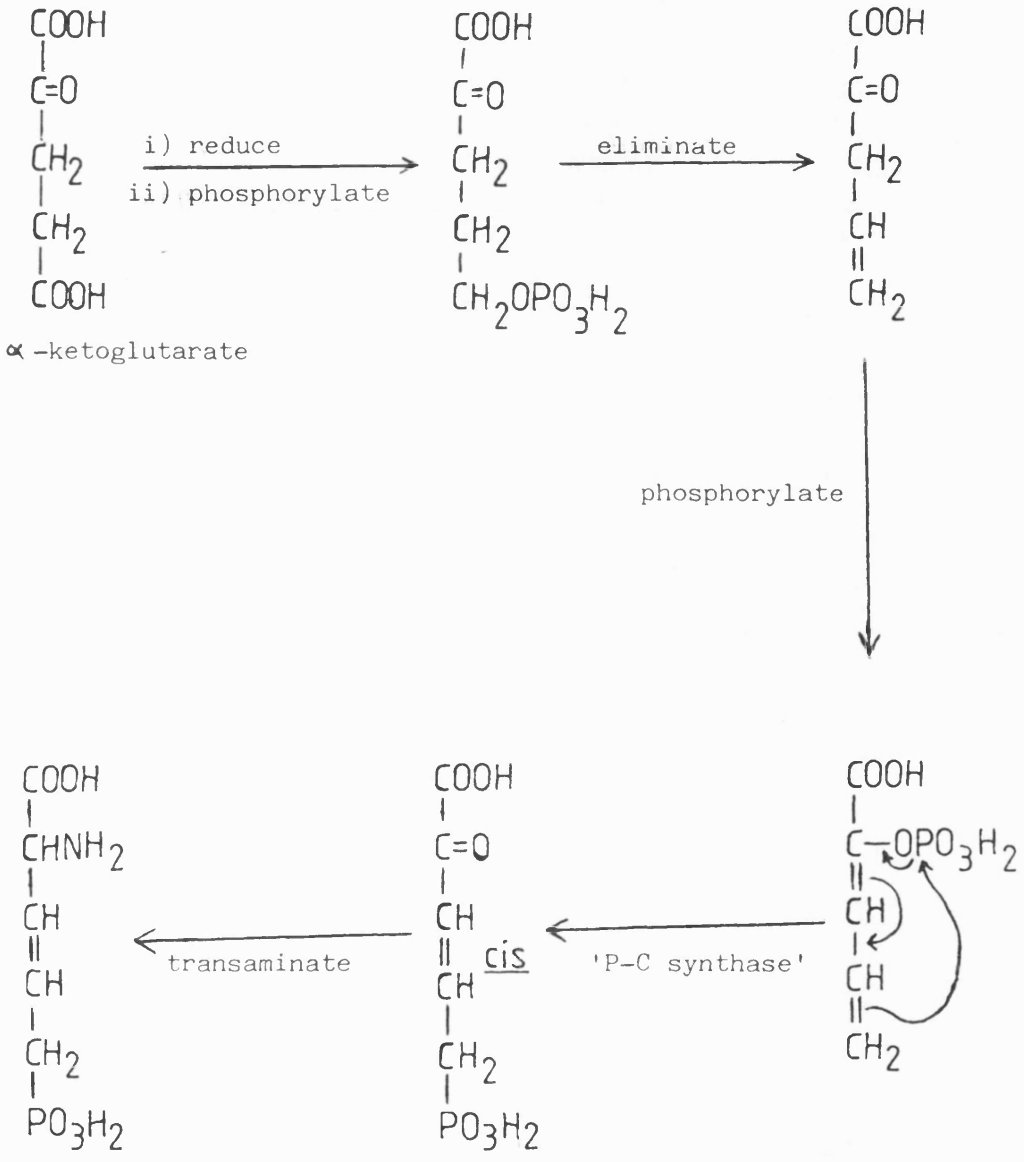


Figure 211

Appendix Three:- Spectra

i ^{1}H nmr of (96)

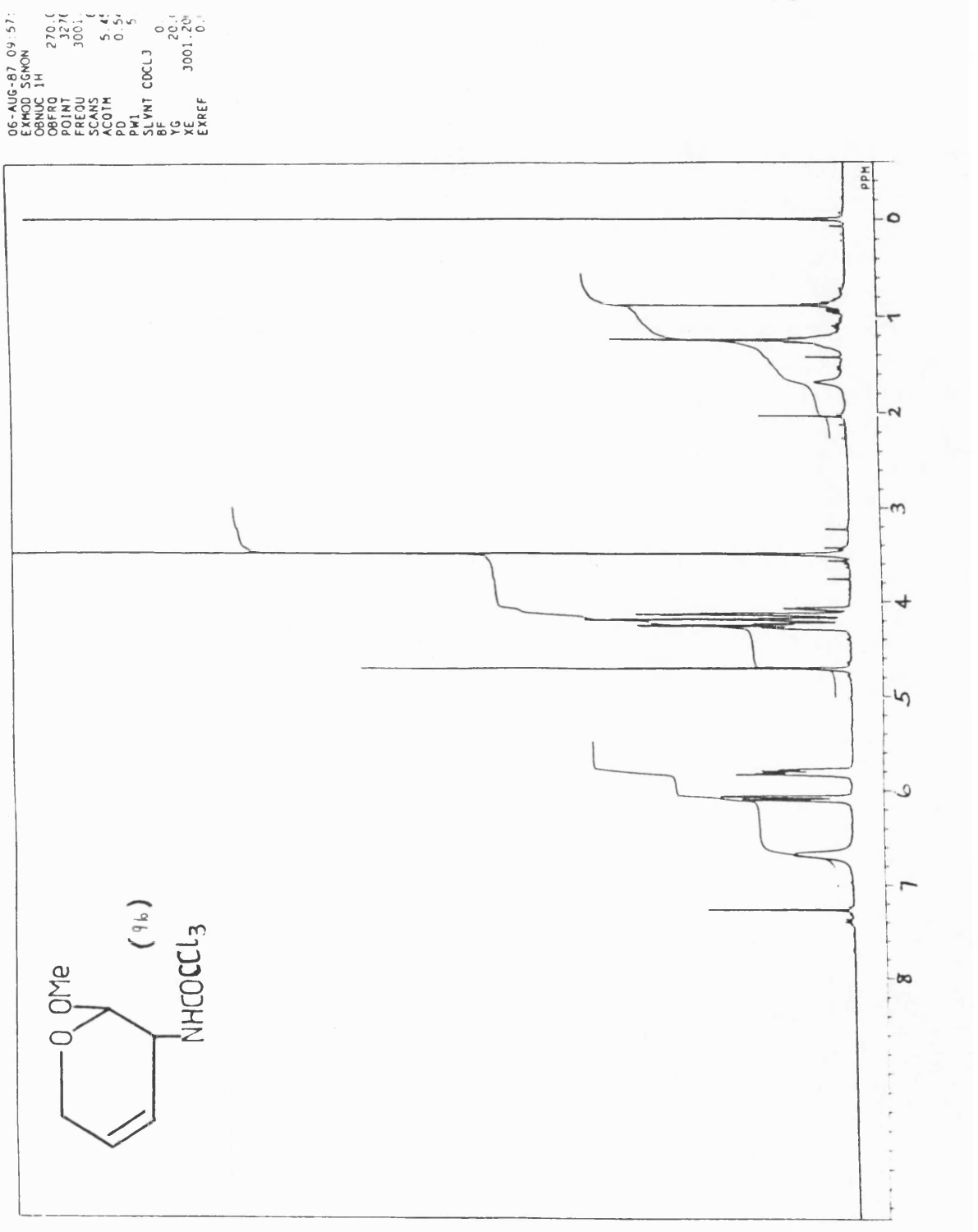
ii COSY of (96)

iii N.O.E. experiment on (96)

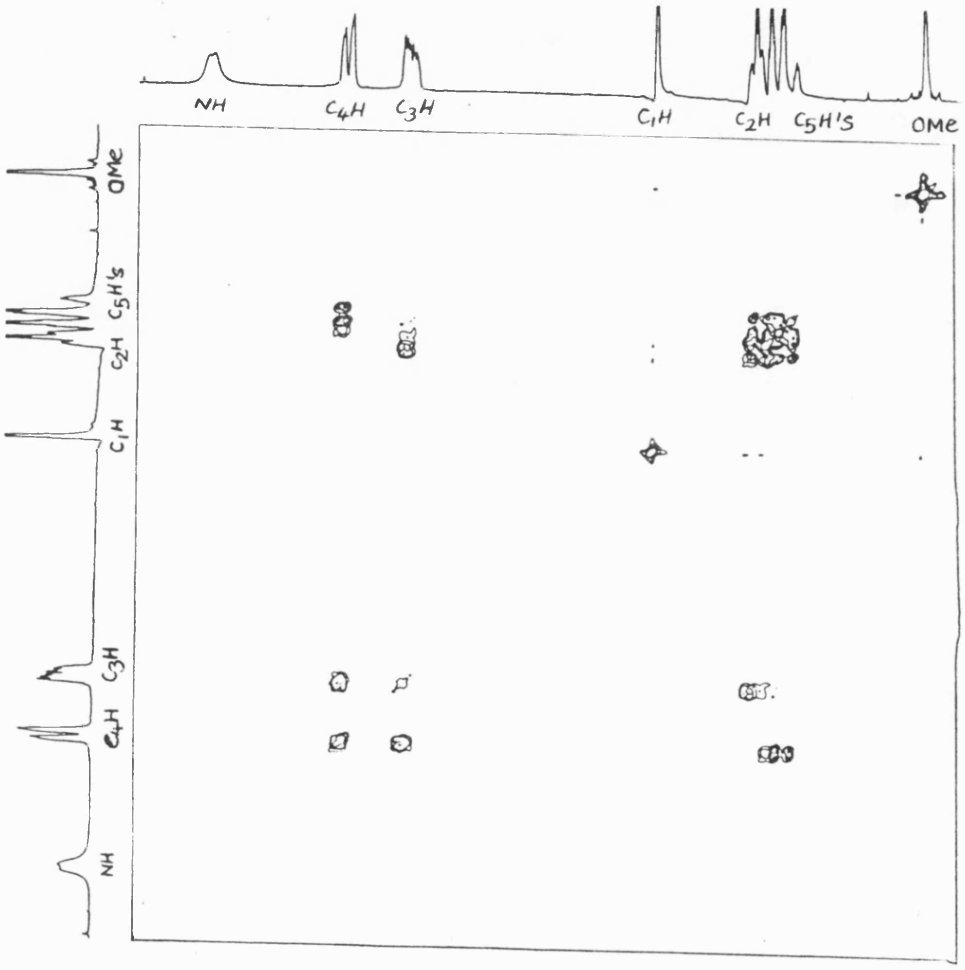
iv ^{1}H nmr of (61)

v COSY of (22a)

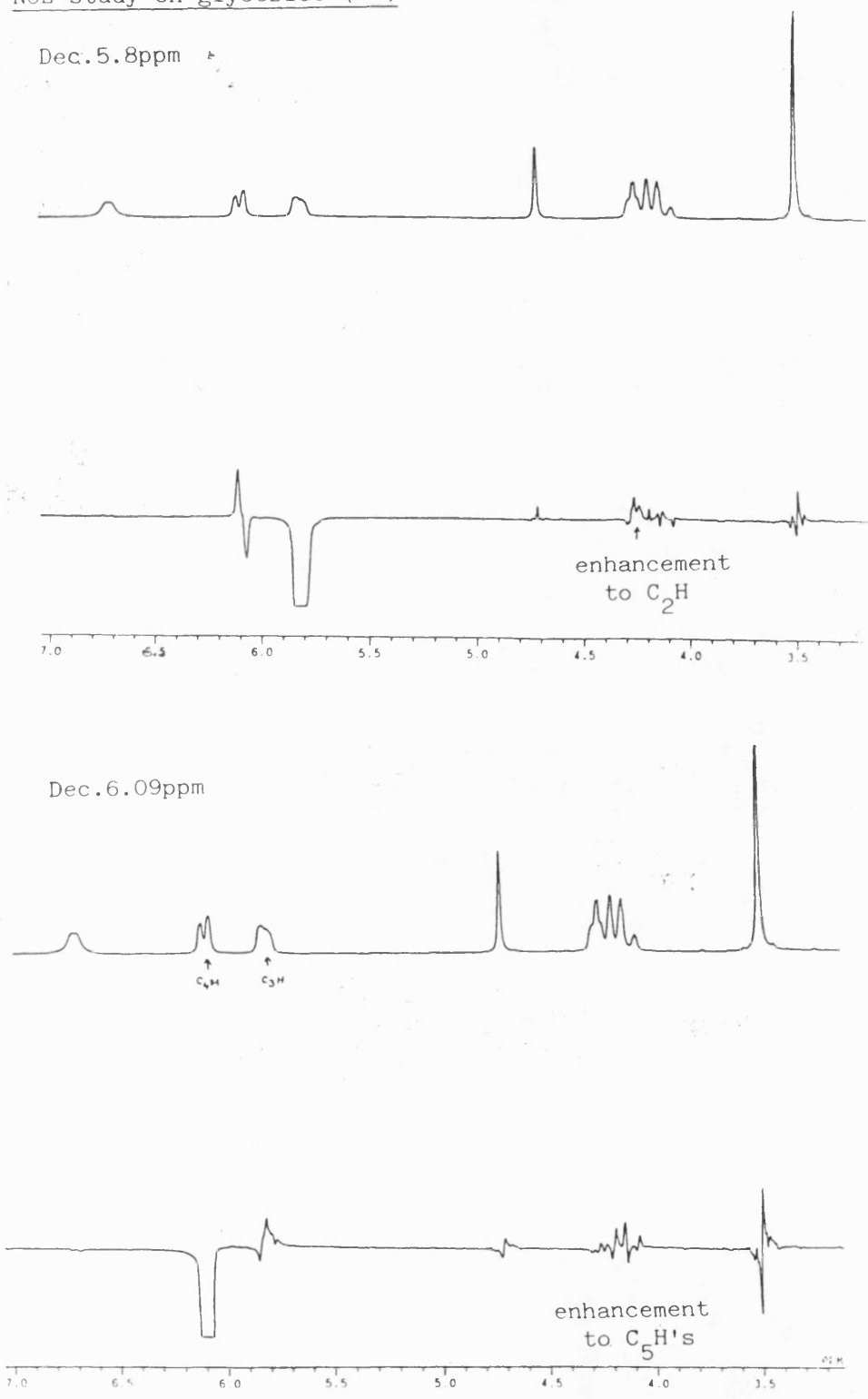
270MHz ^{1}H nmr of the glycoside (96).



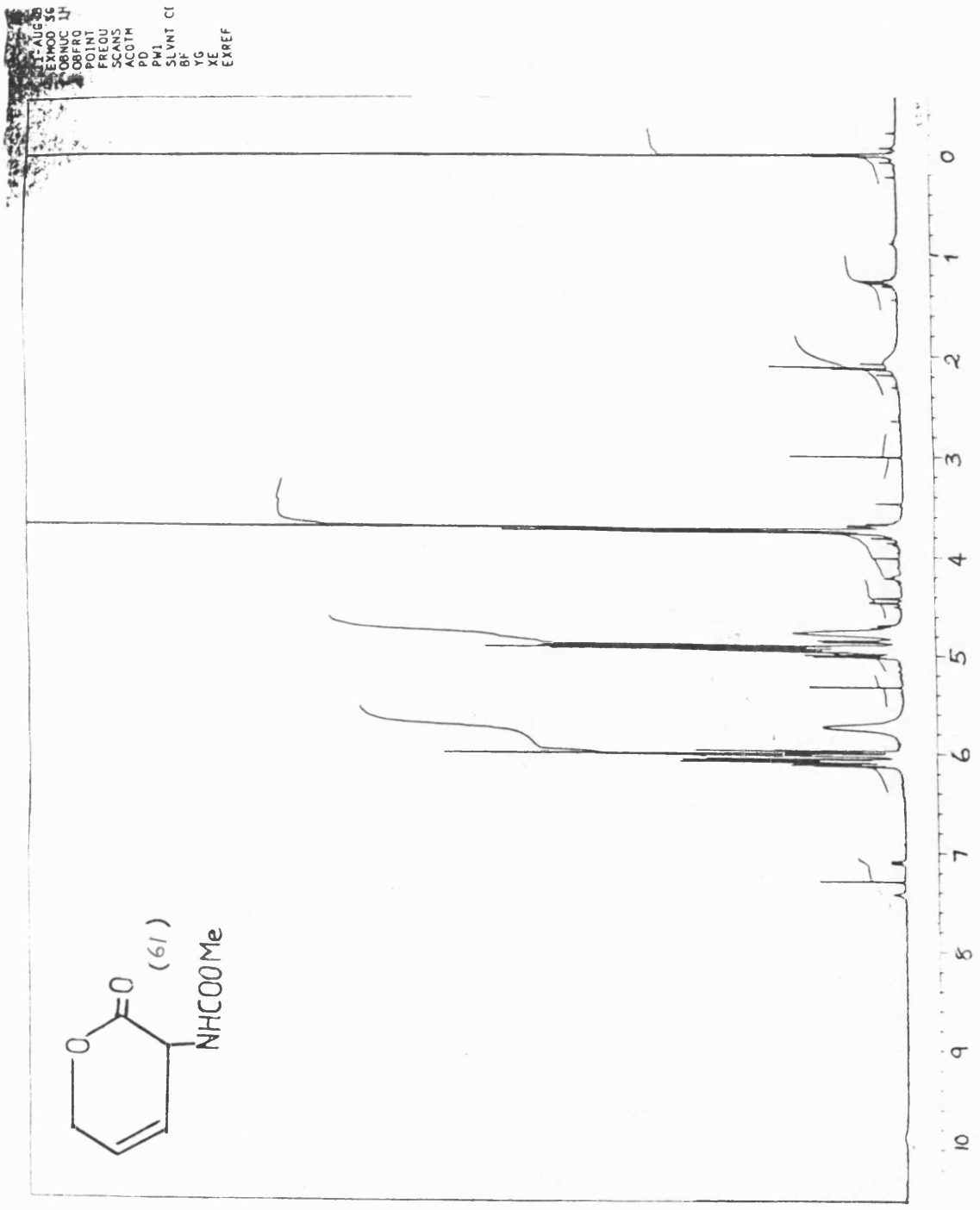
COSY experiment on the glycoside (9b).



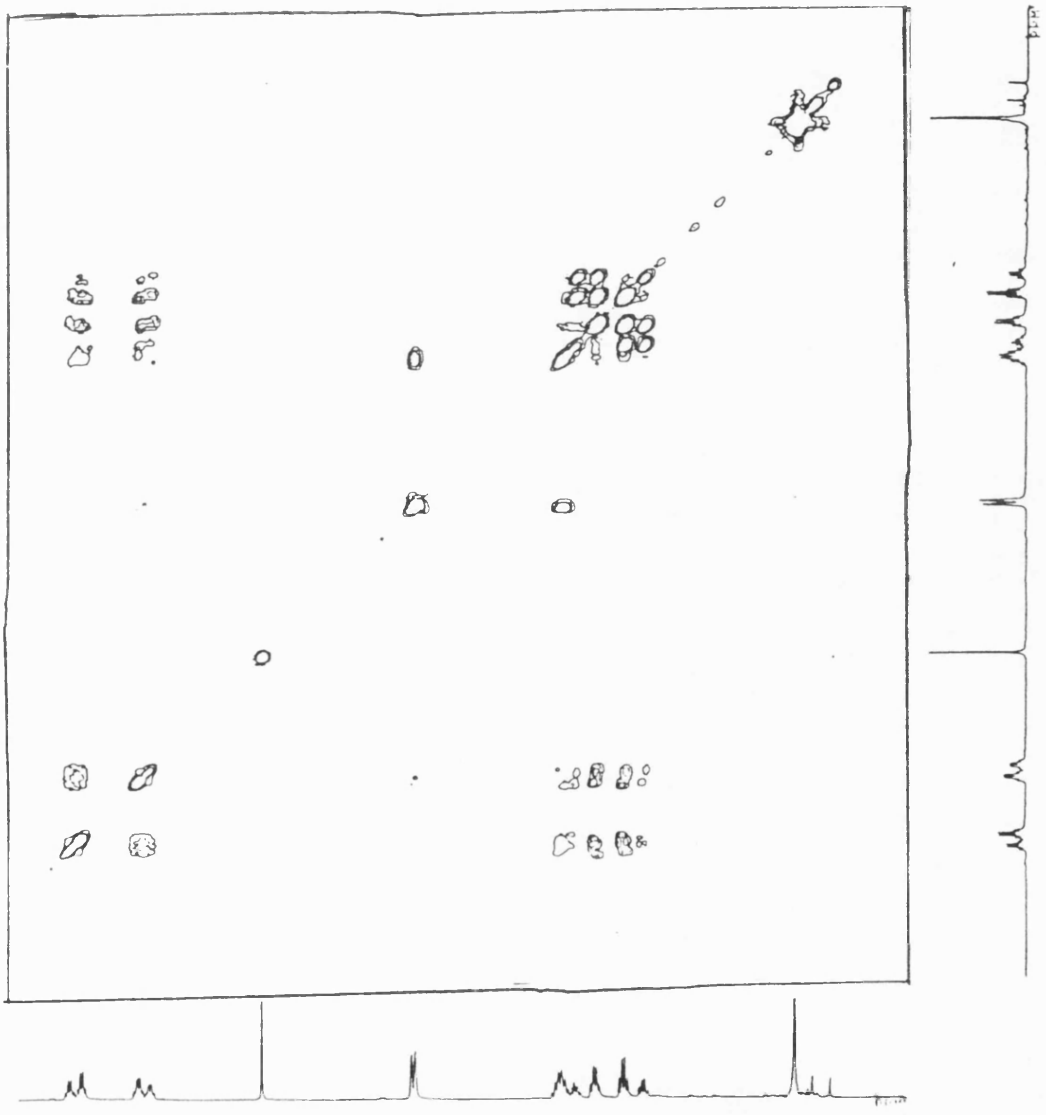
NOE study on glycoside (96)

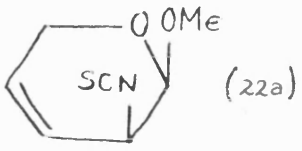


^{1}H nmr spectrum of the lactone (61)



COSY experiment on the isothiocyanate (22a)

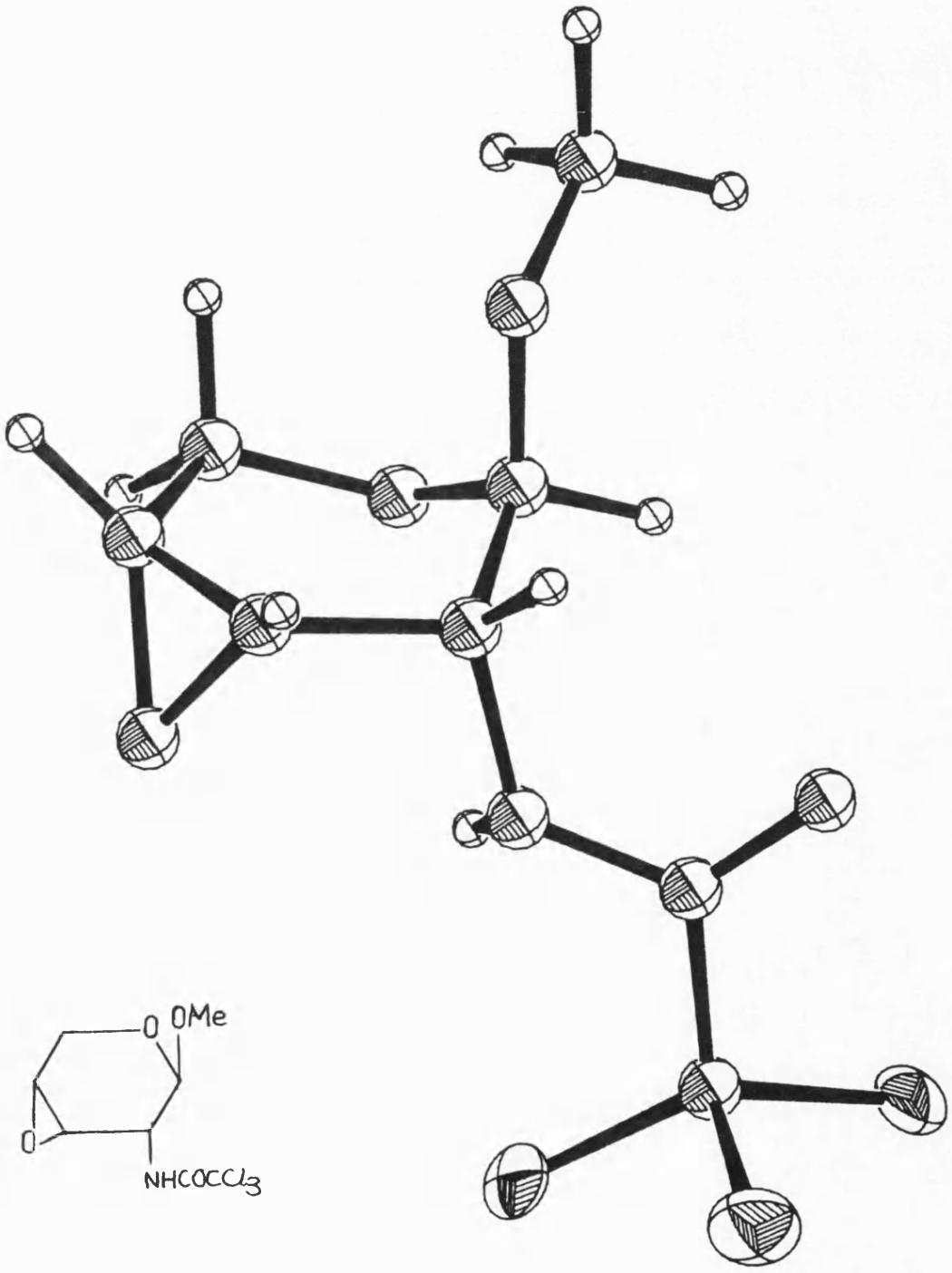




(22a)

X-Ray structure of the epoxide (92)

(With many thanks to Dr Molloy and Mary for their assistance)



Methyl (3*S*,4*R*)-3,4-anhydro-2-deoxy-2-(2',2',2'-trichloroacetamido)-pentopyranoside (92)

Crystallographic Data for (92)

A crystal with approximate dimensions of 0.3x0.3x0.25mm was used for data collection. Analytical data were obtained using a Hilger and Watts Y290 Automatic 4-circle diffractometer.

a= 8.294 (6) , b= 10.983 (5) , c= 12.931 (6) A^{o}

α= 90.0, β= 90.0, γ= 90.0

U= 1177.91, μ= 7.02cm^{-1}, F000= 592.00

Space Group P $2_1 2_1 2_1$

Radiation Mo-Kα (λ = 0.71069 A^{o}), Graphite Monochromator

The structure was solved by direct methods using SHELX86[1] and refined by full matrix least squares using SHELX76.[2] Data were corrected for Lorentz and polarization effects but not for absorbtion. Hydrogen atoms were included in calculated positions. The chlorine atoms were refined anisotropically.

The atomic scattering factors for non-hydrogen and hydrogen atoms and the anomolous dispersion correction factors for non-hydrogen atoms were taken from the literature[3,4,5].

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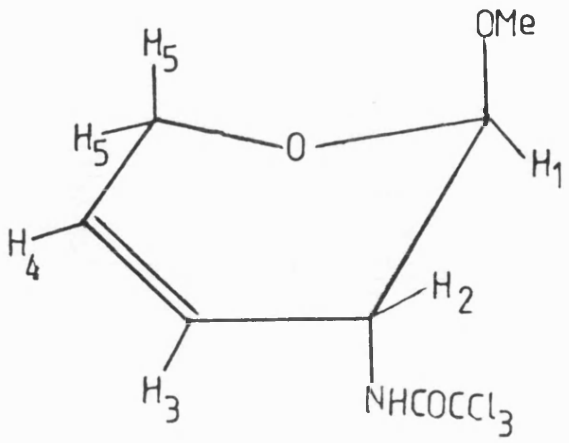
Appendix Five - Complete Structural Assignment of (96)



In order to unambiguously assign each proton in this structure it was necessary to conduct nmr experiments to differentiate between the ends of the double bond.

NH	6.69 ppm
H_1	4.71 ppm
H_2	4.27 ppm
olefinic	5.82 ppm
olefinic	6.08 ppm
H_5	4.23 ppm, 4.12 ppm

NOE DIFFERENCE EXPERIMENT

Saturation of the signal at 6.08 ppm allowed an enhancement to be observed in the signal for the C_5 methylenic unit, suggesting that this signal corresponds to C_4H. Similarly, saturation of the signal at 5.82 ppm showed an enhancement for the C_2H signal, suggesting that this signal corresponds to C_3H.

Having thus fully assigned the proton signals conducting a ^{13}C-^{1}H proton correlation allowed full assignment of the ^{13}C spectrum.

^{13}C-^{1}H CORRELATION

^{1}H nmr		^{13}C nmr
6.69 ppm	NH	-
4.71 ppm	H_1	98.9 ppm
4.27 ppm	H_2	56.1 ppm
5.82 ppm	H_3	120.0 ppm
6.08 ppm	H_4	131.0 ppm
4.23 ppm, 4.12 ppm	C_5H s	58.9 ppm

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